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Selected newer literature from 1986 through 1988 on the vegetation and health effects resulting from exposure to ozone is reviewed and summarized for the purpose of providing the Agency with information useful in identifying new data that may be relevant for developing primary and secondary National Ambient Air Quality Standards for Ozone.

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SUMMARY OF SELECTED NEW INFORMATION ON EFFECTS OF OZONE ON HEALTH AND VEGETATION

Draft Supplement
to
Air Quality Criteria for Ozone and Other Photochemical Oxidants

Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, N.C. 27711

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ABSTRACT

Selected newer literature from 1986 through 1988 on the vegetation and health effects resulting from exposure to ozone is reviewed and summarized for the purpose of providing the Agency with information useful in identifying new data that may be relevant for developing primary and secondary National Ambient Air Quality Standards for ozone.

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SUMMARY OF SELECTED NEW INFORMATION ON EFFECTS OF OZONE ON HEALTH AND VEGETATION

1. INTRODUCTION

The EPA criteria document for ozone and other photochemical oxidants, completed in August 1986, provided comprehensive coverage of the relevant scientific literature on ozone published through mid-1986 (U.S. Environmental Protection Agency, 1986). The criteria document was prepared by the Office of Research and Development (ORD) for the Office of Air Quality Planning and Standards (OAQPS), for use as the scientific basis for the derivation of primary and secondary National Ambient Air Quality Standards (NAAQS) for ozone.

Since completion of the 1986 document, additional information has become available that warrants consideration by the Agency in its current review of the NAAQS for ozone. This summary reviews and evaluates published and "in press" literature pertaining directly to exposure- and dose-response relationships observed in vegetation and in man and experimental animals. Emphasis has been placed on evaluation of the human health effects literature and data potentially useful to the Agency in determining the appropriate form of the secondary standard and the appropriate level and form of the primary standard. Newer data on dosimetry and on exposure-response relationships found in controlled studies in experimental animals have also been included.

The publications reviewed and evaluated in this draft summary have been culled from about 300 new titles and abstracts on the vegetation effects of of ozone and from about 500 new titles and abstracts on the health effects of ozone. The literature base used has been limited to articles appearing in peer-reviewed publications, articles accepted for publication but not yet in print ("in press"), and presentations that will appear in proceedings or journals.

2. EFFECTS OF OZONE ON VEGETATION

2.1 REVIEW OF NEW STUDIES RELEVANT TO SELECTION OF THE AVERAGING TIME FOR THE SECONDARY NAAQS FOR OZONE

A recent review (Hogsett et al., 1988) has outlined the biological, environmental, and exposure-dynamic factors (e.g., concentration, duration, frequency, threshold, respite time) that influence the magnitude of the biological responses of plants. These factors contribute to observed variability in responses, and thus become considerations in measures of exposure that best describe plant response to pollutant exposure. The various types of exposure indices that have been used historically to describe pollutant exposure were also evaluated. The ultimate goal of investigations of factors influencing plant response is to develop exposure indices that account for all of the variation in the exposure-response relationship. However, a second and more practical goal is that of developing or specifying indices useful for standard setting. An index for a standard should be simple, not site-specific, and as generic as possible.

Musselman et al. (1986) examined the influence of two different patterns of ozone exposure on beans. The studies were conducted in a greenhouse and the plants were exposed to either a simulated ambient or a uniform O_3 concentration. The simulated ambient exposures followed the ambient exposure patterns of Riverside, CA (O_3 concentration range: 0.058 to 0.40 ppm; peak exposure duration: 0.5 to 1.5 hr; and total exposure duration: 6 hr). The uniform distribution was selected to match the total dose and peak concentration of the simulated ambient exposure (O_3 concentration: 0.30 or 0.40 ppm; exposure duration: 2.3 hr). Exposures occurred weekly and plants received 1, 2, or 3 exposures; plants were harvested 6 days after their last exposure. Both ozone exposures induced foliar injury and reduced plant growth; however, the effects of the two distributions were not statistically different. Consequently, if the maximum concentrations and "total doses" are equal, peak shape appears not to be an important variable.

Kohut et al. (1988) examined the effect of peak concentration and exposure frequency on the responses of kidney beans to ozone. The plants were exposed to one of four O_3 exposure regimes: (1) constant exposure to 0.05 ppm daily; (2) fluctuating exposure to 0.08 ppm on alternate days (Monday, Wednesday, and Friday); (3) cluster exposure to 0.08 ppm on three consecutive days (Wednesday, Thursday, and Friday); and (4) exposure to 0.12 ppm on two consecutive days (Thursday and Friday) or charcoal-filtered air. The exposure duration was 4 hr and yielded weekly mean concentrations between 0.05 and 0.06 ppm. The test plants were grown in pots and exposed to ozone in open-top chambers under field conditions. Plants were harvested weekly throughout the study. Although there were two replicates of each ozone treatment, the experiment was not replicated in time. In the early harvests, the plants receiving the peak exposures were significantly impaired. By the final harvest (12 weeks), however, there were no significant effects of ozone on any of the plant growth or yield parameters. The authors concluded that the plants integrated the impacts, and, consequently, that "...the response of the plants was related to the mean rather than the peak concentration of exposure." This conclusion is difficult to substantiate with the data, as none of the ozone exposures produced a significant effect at the final harvest. It is therefore not possible to determine whether the various treatments differentially affected plant response.

Heagle et al. (1986) studied the responses of soybeans to chronic doses of ozone applied in two different ways. Plants were grown in the field using standard NCLAN methodology except for the way in which the ozone was dispensed. In one set, various constant amounts of ozone were added to the ambient air for 7-hr/day; for the second set, the ozone was increased above the ambient air by proportional amounts. Although there was a constant addition of O_3 to the ambient air, in the constant-addition treatments the resultant exposure regime was not "square wave" because the O_3 concentration in the ambient air varied throughout the exposure. The principle effect of the constant addition or proportional addition treatments was to create various levels of exposures. The ozone concentrations were expressed as the 7-hr seasonal means. The authors concluded that the two different types of exposure regimes produced identical responses. Several trends in the data, however, cast doubt on the validity of this conclusion. The authors clearly state that the proportional additions caused the more frequent occurrence of elevated concentrations, but their exposure index (the 7-hr seasonal mean) failed to characterize or reflect this elevated exposure. In fact, the 7-hr means for the proportional additions were lower than those for the comparable constant-addition treatments. The authors also reported that the slope of the "dose-response curve" for the proportional additions was greater than for the constant additions. The authors speculated that an extension of the dose range might have shown significant results. The failure of the 7-hr seasonal mean to characterize adequately the higher concentrations is not surprising, since a previous paper (Cure et al., 1986) from the same group states that the 7-hr seasonal mean was selected specifically because it was less sensitive to variations in ozone patterns. Consequently, the conclusions of the authors must be viewed with skepticism.

Heagle et al. (1987) evaluated the influence of daily ozone exposure duration and fluctuations in concentrations on tobacco yield. Plants were grown in the field using standard NCLAN methodology except for the ozone-dispensing protocol. In one set of studies, various constant amounts of ozone were added to the ambient air for 7-hr/day; to the second set, the ozone was increased above the ambient air by proportional amounts. In addition, the study compared the effects of 7- and 12-hr exposures on tobacco yield. The ozone concentrations were expressed as the 7- and 12-hr seasonal means. Yield was reduced to a greater extent by 12-hr than 7-hr exposures. The authors concluded that the two different types of 7-hr exposure regimes (7-hr constant and 7-hr proportional) produced identical responses.

Rawlings et al. (1988) conducted additional analyses of the soybean (Heagle et al., 1986) and tobacco (Heagle et al., 1987) data sets to evaluate various exposure indices and the influence of exposure duration on plant response. The results from the soybean data and the 12-hr studies with tobacco suggested that the peaks should be given greater weight. In contrast, the 7-hr studies with tobacco suggested that the arithmetic mean was sufficient and that the peaks did not require additional weighting. Rawlings et al. acknowledged that these results must be viewed with caution as the differences in exposure profiles between the constant and proportional ozone additions were relatively small, thus limiting the power of the experiment for determining the "best" exposure index. This same caveat also applies to the conclusions reached by the authors of the soybean (Heagle et al., 1986) and tobacco (Heagle et al., 1987) studies. The analysis of exposure duration found that 12-hr exposures caused greater effects than 7-hr exposures (Rawlings et al., 1988). The negative impact of the exposures did not increase linearly with exposure duration; i.e., the decrease in yield loss was not directly proportional to the increased length of exposure.

In a study by Adomait et al. (1987), white beans (Phaseolus vulgaris) were grown in field plots throughout southern Ontario, Canada. Plants at each location were treated with a chemical protectant (EDU) to reduce or eliminate the impact of ozone on yield, which was determined as the difference between the yields of EDU and non-EDU treated plots at each location. Ozone exposure was expressed as the cumulative ozone concentrations above a threshold of 0.08 ppm for the month of August. Yield decreased as the cumulative ozone concentration increased. The addition of temperature and rainfall to the regression equation, in an attempt to approximate ozone flux into the plant, significantly improved the fit of the regression equation to the data. To express the experimental results, the authors assumed that the elevated ozone concentrations (peaks) were important and that the impact was the cumulative result of multiple exposures.

Data used in a study by Cure et al. (1986) were generated using standard open-top chamber NCLAN protocols. The study did a three-way comparison of relationships among the 7-hr seasonal mean, the 1-hr seasonal mean, and the 1-hr maximum for the season. For two of the three comparisons, the 7-hr/1-hr ratio was essentially constant, suggesting that these two variables differed by a constant. For the other comparison, the ratio was less stable. The authors concluded, however, that the 7-hr and 1-hr seasonal means were surrogates for each other. The ratio of the 1-hr maximum to the 7-hr seasonal mean was highly unstable, which suggests that the maximum was poorly related to the long-term mean. The authors selected a seasonal mean for two reasons: (1) They assumed that crop yield reductions resulted from an accumulation of daily ozone effects over the growing season; and (2) the seasonal means were much less sensitive to peak variations in yearly ozone patterns, especially at concentrations near the current ambient levels.

In a study by McCool et al. (1986), plants grown in a standard soil were exposed to a range of ozone levels in closed-top exposure chambers and the yields were determined. The authors developed yield-loss functions which related decreased crop yield to a cumulative exposure index for 12 crops. Ozone exposure was characterized as the cumulative concentrations greater than 0.10 ppm. The concentration threshold (0.10 ppm) was chosen because it was the California state ozone standard. A threshold concentration for 0^3 was used to avoid giving equal mathematical weight to the numerous low concentrations and to ignore the low nighttime background in calculating the exposure.

In a field study using closed-top exposure chambers, McCool et al. (1987) assessed the impact of ozone on four vegetables (turnip, beet, onion, lettuce).

The exposure-response functions were best described as a linear function with increasing exposure. Both the sum of the concentrations >0.10 ppm and the 12-hr seasonal mean concentration were used in developing the exposure-response functions. Neither exposure index was uniformly best.

A 3-year field study was conducted by Smith et al. (1987) in which the effects of ozone on foliar injury and yield were assessed using the chemical protectant, EDU. Ozone exposure was characterized as the 7-hr seasonal mean and as the cumulative exposure (using various concentration thresholds). The EDU treatment did not significantly enhance crop yield. Yield and foliar injury, respectively, were similar among cultivars and over years. Although the ambient ozone exposures between 1983 and 1984 were substantially different, as indicated by the various cumulative statistics, this difference was not reflected in the 7-hr seasonal mean. These data are another example of the lack of sensitivity of the mean to temporal variations in ozone exposures.

Open-top chambers were used by Wang et al. (1986a) in a field study to examine the effects of ambient ozone on the growth and foliar injury of three tree species. Ozone was characterized as the number of daily occurrences above 0.08 and 0.12 ppm. The authors concluded that ozone significantly impaired the growth of hybrid poplar in the absence of visible foliar injury. There were 20 days when ozone exceeded 0.08 ppm and 1 day when the concentration exceeded 0.12 ppm. In a 3-year study with quaking aspen, Wang et al. (1986b) found that plant growth was reduced 12 to 24%. In only one of the years was the current national ambient air quality standard for ozone exceeded. The observations that growth reductions can occur in the absence of the ambient O_3 concentration exceeding the level of the current standard are consistent with the recent analysis of Lee et al. (1988b), which forecast significant effects on crop yield when the standard was not exceeded.

Only a limited number of studies have been conducted with the specific objective of developing or evaluating various exposure indices; several studies have reanalyzed existing exposure-response data to evaluate a range of exposure indices. The results of these retrospective analyses have provided useful concepts and their conclusions are in general agreement. Because the experiments analyzed were not specifically designed to evaluate various indices, the differences among the actual exposure treatments (frequency of ozone occurrences) may be relatively small. Consequently, the power of these studies is less than desirable.

Reanalysis of several NCLAN data sets (soybean and wheat from Argonne, IL; cotton from Shafter, CA; and alfalfa from Corvallis, OR) was performed by Lee et al. (1987) using various mean and cumulative peak-weighted exposure indices (e.g., concentration threshold and functional peak weighting). Exposure indices that included all the data (24 hr) performed better than those that used only 7 hours of data. The 7-hr seasonal mean was never "best" and was near optimal in only 5 of 14 cases. From a modeling standpoint, the exposure indices that emphasized peaks performed better than those that gave equal weighting to all concentrations; indices that accumulated the exposures performed better than those that averaged the exposures.

In a more extensive retrospective analysis of NCLAN data, Lee et al. (1988a) fit 24 common and 589 general phenologically weighted, cumulative-impact (GPWCI) exposure indices to the response data from seven crop studies (2 years of data for each). The "best" exposure indices were those that displayed the smallest residual sums of square error when the yield response data were regressed on the various ozone exposure indices using the Box-Tidwell model. The "best" exposure index was a GPWCI with sigmoid weighting on concentration and a gamma weighting function as a surrogate for changes in plant sensitivity over time. Cumulative indices (with concentration thresholds) performed as well as the GPWCIs, while mean indices did not perform as well. The general conclusions of the authors were, "While no single index was deemed 'best' in relating ozone exposure to plant response, the top-performing indices were those indices that (1) cumulated the hourly ozone concentrations over time, (2) used a sigmoid weighting scheme which emphasizes concentrations of 0.06 ppm and higher, and (3) phenologically weighted the exposure such that the greatest weight occurs during the plant growth stage. These findings illustrate the importance of the duration of exposure, the importance of repeated peaks, and the time of increased sensitivity in assessing the impact of ozone on plant growth." Although peak concentrations should be given greater weight, the authors suggested that lower concentrations should also be included but given lesser weight in the calculation of an exposure index.

The paper by Tingey et al. (1988) is essentially a condensation of the paper by Lee et al. (1988a) and therefore the conclusions are basically the same. However, the paper does show the importance of exposure duration in influencing the magnitude of plant response and the limitation of the seasonal mean to specifically incorporate varying exposure durations. For example, the mean can not distinguish among exposures to the same average concentrations over different durations (e.g., for 10, 50, or 100 days).

Wheat and soybean data sets (Kohut et al., 1987, 1986) collected using standard NCLAN protocols at Ithaca, NY, were reanalyzed by Lefohn et al. (1988a) to compare exposure indices. The authors used the 7-hr mean and cumulative statistics with thresholds, or peak weighting. The data were fit with both linear and Weibull response models. No one exposure statistic was best for all data sets or response models. The linear model showed no strong tendency to fit any exposure index; however, a peak-weighted statistic and the number of occurrences, >0.08 ppm or the sum of the concentrations >0.08 ppm had a higher R2 than the 7-hr seasonal statistic. When the Weibull model was used, the cumulative statistics performed better than the seasonal means. The authors also concluded that a sigmoid peak-weighted scheme was better than a threshold approach because it included the effects from the concentrations below the selected threshold concentration but gave them less weight.

The paper by Lefohn et al. (1988a) has engendered discussion in the literature about the interpretation of the data (Runeckles, 1988; Parry and Day, 1988). Both groups of respondents thought that the paper contained insufficient data and evidence to support the conclusion that peak-weight exposure indices should be used in developing exposure-response functions. However, Runeckles tempered his criticism with the observation that peak-weighted indices performed at least as well as mean indices. Also, the respondents criticized the compilation of the 2 years of wheat data into a single model when the exposure durations were markedly different. In response, Lefohn et al. (1988b) stated that the wheat data support the need to include a cumulative component in an exposure index. They concluded that, "The cumulative index is more relevant to use in the standard-setting process than seasonal means, which ignore the length of the exposure period."

Musselman et al. (1988) conducted a retrospective analysis of crop loss data originally collected by R. Oshima (see U.S. Environmental Protection Agency, 1986). The analysis was based on data for five crops but those data were not replicated in time. The plants were grown in pots in standardized soil and provided with adequate water and nutrients. The plants were placed at 9 to 12 sites along an ambient ozone concentration gradient in the Los Angeles Basin. The crop loss data were originally summarized by Oshima on the basis of the cumulated concentration above 0.10 ppm for the growing season. In this study, the authors tested (1) various peak indices, (2) daily mean indices, and (3) indices based on subsets of a 24-hr day. No single exposure index was "best" for the five crops. Ozone indices utilizing a concentration threshold level performed well for most crops, but the optimum threshold level varied with the particular index calculated. Some of the "better" indices were: (1) seasonal mean of concentrations above 0.09, 0.12, or 0.14 ppm; (2) mean of all daily peak concentrations; (3) sum of the daily peaks squared above a concentration of 0.15 ppm; and (4) total number of seasonal peaks above 0.12 ppm. The 7- or 12-hr seasonal means were not among the better-performing indices.

Larsen et al. (1989) evaluated 14 ozone exposure indices for their ability to predict crop yield loss. The second highest daily maximum concentration and 13 other indices, including the effective mean ozone concentration and the summer daytime average (M7), were calculated for 80 "agricultural" National Aerometric Data Bank sites and for multiple years, for a total of 320 site-years. In contrast to other retrospective analyses, separate exposure-response functions were not derived from biological data for each exposure index. Larsen et al., (1989) used ambient air monitoring data to derive correlations between the effective mean and other air quality indices. These correlations (based only on ambient air monitoring data) were used to express the plant response data in terms of the different indices, i.e., the lognormal model that expressed crop reduction as a function of the effective mean concentration (Larsen and Heck, 1984) was used to generate crop loss estimates for the 320 site-years of ambient data. Since there was no biological variation in the data, correlations between the exposure indices and estimated crop reductions were, in fact, measures of association between the (transformed) effective mean and the other indices. Consequently, no evidence that the mean indices were better correlated with plant response than other indices can be inferred from the analysis of Larsen et al.

Larsen et al. (1983) developed an exposure-response model that relates O_3 impact on plants to a cumulative index that they denoted as the total impact. A 75-day exposure for 7 hr/day was originally assumed for calculating the estimated crop reduction for soybean (this may not be representative of the phenological life span of soybean). In the original analysis, the effective mean was not calculated from the hourly ozone concentrations for the NCLAN studies but was estimated by multiplying M7 by 1.15 for charcoal-filtered (CF) and non-filtered (NF) exposures (and supplementing the NF exposures with the constant additions for other exposures). Further, treatment means rather than chamber means were used in estimating the lognormal model. Consequently, this lognormal model is inaccurate and needs to be estimated more precisely for use in the selection of exposure indices for use as a O_3 standard. The adequacy of the lognormal model using other exposure indices must also be determined.

Reich and Amundson (1986) have reviewed a series of field and controlled-environment studies to assess the impact of ozone on photosynthesis. The authors stated, "...it may be inappropriate as well as difficult to compare directly the response of the species on the basis of a mean O_3 exposure concentration. However, when the responses are compared on the basis of a unit dose of O_3, the results are more easily interpreted." A unit dose of O_3 as defined by the authors means cumulative exposure, i.e., total ppm. The ozone-induced decrease in growth was directly related to reduced photosynthesis, which was decreased by the cumulative ozone exposure.

2.2 SUMMARY AND CONCLUSIONS: NEW VEGETATION EFFECTS DATA

Recent literature concerning the appropriate averaging time for an exposure index was evaluated in relation to: (1) the role of exposure duration; (2) the role of peak concentrations; (3) comparison of exposure indices; and (4) evaluation of the 7-hr seasonal mean.

2.2.1 Exposure Duration

Increasing the duration in the exposure index from a 7-hr seasonal mean to a 12-hr seasonal mean caused a greater decrease in yield. A comparison of 7- and 24-hr exposure indices showed that 24-hr indices provided an even better statistical fit to the exposure-response data. Although plant effects increased with exposure duration, the study of Rawlings et al. (1988) showed that the increase in plant response was not proportional to the increase in exposure duration.

All the recent studies that used impaired plant growth or yield as an adverse effect specifically selected exposure indices that might reflect the cumulative impact of effects throughout the growing season. For example, Cure et al. (1986) stated that crop yield reductions result from an accumulation of daily ozone effects over the growing season. Reich and Amundson (1985) stated that the ozone-induced decrease in growth was directly related to reduced photosynthesis, which was impaired by the cumulative ozone dose. These data can be interpreted to mean that growth and yield are reduced by repeated ozone episodes, because that is how ozone occurred in the studies and how it occurs in nature.

The recent studies support the conclusion that a cumulative ozone exposure index is needed that reflects the total exposure that the plant experiences. This conclusion is consistent with the recent EPA criteria document (U.S. Environmental Protection Agency, 1986), which states, "When plant yield is considered, the ultimate impact of an air pollutant on yield depends on the integrated impact of the pollutant exposures during the growth of the plant." By inference or deduction, then, a mean of unspecified time (days, or months) is inappropriate since the lack of specification of "time" results in a variable duration of O_3 accumulation.

2.2.2 Peak Concentrations

Most of the recent studies, except for papers reporting results of the NCLAN program, selected exposure indices that cumulated the exposure and preferentially weighted the peaks. Three main peak-weighting approaches have been used: (1) a concentration threshold approach, in which the concentrations above the selected threshold are summed; or in which the number of days or hours above the concentration threshold are summed; (2) an allometric or exponential weighting, in which all concentrations are raised to a specific exponential power; and (3) a sigmoid weighting, in which all concentrations are weighted with a multiplicative weighting factor (which depends on concentration).

The threshold weighting approach assumes that only the concentrations above the selected concentration threshold are biologically active. Recent studies have shown that the concentrations below the selected concentration threshold or cutoff may also have biological importance. It is also likely that the appropriate concentration threshold differs between species, with environmental conditions, and with endpoint measured.

Functional weighting approaches using either an allometric or sigmoid weighting are preferred to the concentration threshold approach. These approaches do not censor concentrations, but rather give weight, although not equal, to all concentrations in eliciting a biological response. Specific comparisons of the functional weighting to the threshold approaches showed that they yielded better statistical fits to the data. Also, the sigmoid weighting functions appeared to perform better than the allometric weighting approach.

The conclusions found in recent literature regarding the importance of cumulative peak concentrations in causing vegetation responses are consistent with the data and conclusions presented in the recent criteria document (U.S. Environmental Protection Agency, 1986a).

2.2.3 Comparison of Exposure Indices

There have been several studies (Lee et al., 1987, 1988a,b; Lefohn et al., 1988a; Musselman et al., 1987) conducted that were retrospective analyses of existing plant-response data sets. These authors evaluated the relative efficacy of existing and proposed exposure indices, using a large number of crop data sets. The exposure indices included various means, and cumulative statistics using both threshold and functional concentration weighting. The authors concluded that there was no single exposure index that was best for all crop species or for all data sets. These studies are all in agreement, however, that (1) mean indices are not among the best indices and (2) the preferred (yielded best statistical fit to the data) exposure indices cumulated the exposure impact over the growing season and preferentially weighted the peak concentrations.

2.2.4 Evaluation of the 7-hr (or 12-hr) Seasonal Mean

The 7-hr seasonal mean is the most commonly used exposure index in the literature reviewed in the recent EPA criteria document (1986), and it continues to be used by investigators. Mathematically, the mean contains all hourly concentrations making up the exposure period and treats all concentrations equally, thus implying that (1) all concentrations of ozone (across the range of concentrations to which plants are exposed in a growing season) are equally effective in causing a response; and (2) minimizes the contributions of the peak concentrations to the response. The mean treats low-level, long-term exposures the same as high-concentration, short-term exposures, a scenario that the literature does not support (e.g., the recent EPA criteria document). An infinite number of hourly distributions, from those containing many peaks to those containing none, can yield the same 7-hr seasonal mean. Cure et al. (1986) reported that mean characterizations of ozone exposure were much less sensitive than the daily 1-hr maximum to variations in yearly ozone patterns.

Also, Reich and Amundson (1985) stated, "...it may be inappropriate as well as difficult to compare directly the response of species on the basis of a mean O_3 exposure concentration. However, when the responses are compared on the basis of a unit dose of O_3, the results are more easily interpreted."

The use of a mean exposure index for characterizing exposures implies certain assumptions:

1. A seasonal mean assumes that crop yield reductions result from the accumulation of daily ozone effects over the growing season (Cure et al., 1986).
2. A mean assumes that the distribution of hourly ozone concentrations (over the averaging time) are not highly skewed and that the distribution is unimodal. In the ambient, the ozone concentration distributions are frequently skewed toward the higher concentrations.
3. The mean weights all concentrations within the selected averaging time equally.
4. The mean does not specifically include an exposure duration component; it cannot distinguish between two exposures to the same concentration but of different durations (e.g., 50 or 100 days).
5. The mean assumes that the selected time interval, over which the concentrations are averaged, is the period of highest hourly occurrences of ozone or any other pollutant being examined.
6. The mean index assumes that peak events do not need to be given special consideration. This is not consistent with results showing that short-term peak concentrations are important in determining vegetation response (see, e.g., the recent EPA criteria document).

The correlation between the 7-hr seasonal mean (M7) and the second-highest daily maximum 1-hr concentrations (i.e., HDM2, the current O_3 standard) was low (r=0.54) due to the insensitivity of peak concentrations in the M7 calculation (Lee et al., 1988b). A wide range of temporal distributions with HDM2 between 0.06 and 0.24 ppm was found at sites with M7 values between 0.036 and 0.048 ppm. Temporal distributions of ambient O^3 data at 83 nonurban sites showed large spatial differences, across these sites with the HDM2 ranging from 0.06 to 0.24 ppm. In contrast, the 7-h seasonal mean (M7 calculated from May to September) across the 83 sites showed small differences, i.e., 90% of the sites had M7 values between 0.03 and 0.06 ppm.

3. EFFECTS OF OZONE ON HEALTH

3.1 REVIEW OF NEW HEALTH STUDIES RELEVANT TO SELECTION OF THE PRIMARY NAAQS FOR OZONE

3.1.1 Human Controlled Studies

The strongest and most quantifiable concentration-response data on the health effects of ozone are provided by the controlled human exposure studies, in which significant decrements in pulmonary function have been reported (U.S. Environmental Protection Agency, 1986). In most of these studies, the greatest attention has been focused on decrements in forced expiratory volume (FEV_1), since this measure of lung function represents a summation of changes in both lung volume and resistance. At the lower ozone concentrations of interest for standard-setting, however ($\geq$0.12 ppm), the observed decrements in FEV_1 primarily reflect decrements in forced vital capacity (FVC) with little or no contribution from changes in airway resistance. These changes in FEV_1 are caused by a reduced inspiratory capacity that most likely results from sensitization or stimulation of airway irritant receptors.

Scientific evidence presented in the EPA criteria document established that pulmonary function decrements are generally observed in healthy adults after 1 to 3 hr of exposure as a function of the level of exercise performed and the ozone concentration inhaled during the exposure. Decrements in lung function have been reported to occur in some groups of healthy adults at the current level of the standard (0.12 ppm) or somewhat higher. Also, pulmonary function decrements have been observed in children and adolescents at concentrations of 0.12 ppm and 0.14 ppm, respectively, with heavy exercise. At the lower O_3 concentrations in the range 0.12 to 0.16 ppm, the average group mean changes in lung function are generally small ($\leq$6 percent) and the medical significance of these changes is a matter of controversy. Some individuals, however, are intrinsically more responsive to ozone than others and exhibit noticeably larger-than-average pulmonary function decrements than the rest of the group. Such larger (>10 percent) decrements in lung function may be of some medical significance to the affected individuals.

Two recent studies, by Linn et al. (1986) and Avol et al. (1987), add to the information currently reviewed in the EPA criteria document on lung function changes occurring in healthy children and young adults exposed to low concentrations of O_3 while exercising at moderate to heavy loads (see Table 1).

TABLE 1. NEW CONTROLLED HUMAN LABORATORY AND FIELD STUDIES RELEVANT TO REVIEW OF THE 1-HR NAAQS FOR OZONE

Ozone Concentration µg/m³	Ozone Concentration ppm	Exposure Duration and Activity[a]	No., Sex, and Age of Subjects	Observed Effects	Conclusions	Reference
0 221	0.00 0.113[b]	1 hr CE (22 L/min) 33°C and 43% rh	66 children 33 M, 33 F 8-11 yr old	Forced expiratory function and symptoms in the group showed no statistically significant responses to 0.113 ppm O_3 in ambient air when compared to purified air; there were no gender differences. Regression analysis of individual data indicated a significant ($p < 0.05$) trend toward decreased forced expiratory function with increasing O_3 concentration.	The responsiveness of children to ambient ozone exposure is qualitatively similar to that of adolescents and adults although definitive comparisons among age groups were not possible because of differing ambient exposure levels and large intersubject variability in responsiveness to ozone.	Avol. et al. (1987)
0 882	0.00 0.45	2 hr, IE (20/20) 26 L/min 3 exposures	8 M, 8 F 51-76 yr old	Group mean changes in FVC were similar for the three exposures (-4.6, -5.8, -4.2%) but individual responses were variable.	In older subjects, ozone responsiveness may be variable from time to time.	Bedi et al. (1988)
0 882	0.00 0.45	2 hr, IE (20/20) 25 L/min	8 M, 8 F 51-76 yr old 8 M, 8 F 19-26 yr old	Decreases in spirometry were slightly greater in older women (FVC = 7.1%; FEV_1 = -7.0%) than in older men (-3.5%, -4.2%) despite higher average $\dot{V}_E$ in men. Ratio of exercise $\dot{V}_E$ to FVC was larger in women (9.5) than men (6.3). Older subjects FVC = -5.3%; FEV_1 = -5.6%) had less response than young subjects (FVC = -14.1%; FEV_1 = -17.8%) under same exposure conditions.	Spirometry effects in older subjects are smaller than in younger subjects for similar ozone exposure	Drechsler-Parks et al. (1987) Drechsler- Parks et al. (1988)
0 784	0.0 0.4	2 hr, IE (30 L/min/m², ~53 L/min)	10 normal 18-35 yr old	(See also Kreit et al., 1988). Subjects were exposed to ozone with no medication, placebo, or indomethacin prior to exposure. Changes in FVC were -19.1, -12.6, -6.8% respectively. In previous study with the same protocol (Kreit et al.), FVC change was -9.4%. Spirometry changes in this group of normal subjects were greater than in the asthmatics. Indomethacin reduced FVC change but did not alter change in airway response to methacholine.	Indomethacin partially blocks ozone-induced restrictive pulmonary function changes but not changes in airway responsiveness.	Eschenbacher et al. (1988)

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TABLE 1. (cont'd) NEW CONTROLLED HUMAN LABORATORY AND FIELD STUDIES RELEVANT TO REVIEW OF THE 1-HR NAAQS FOR OZONE

Ozone Concentration µg/m³	ppm	Exposure Duration and Activity[a]	No., Sex, and Age of Subjects	Observed Effects	Conclusions	Reference
0 235	0.00 0.12	6.6 hr IE (40 L/min) (6) 50-min exercise periods + 10-min rest; 45-min lunch 18°C and 40% rh	10 males 18-35 yr old	Forced expiratory and inspiratory spirometry measured before exposure and after each exercise period demonstrated a progressive fall in lung function during the 6.6 hr exposure to 0.12 ppm O_3; FEV_1 decreased 13.6%, FVC decreased 8.5%, and $FEF_{25-75\%}$ decreased 17.4% by the end of exposure. FIVC and $FIV_{0.5}$ were decreased 12.6% and 20.7%, respectively. No changes were observed with clean air exposure. Increases in the symptom ratings of cough and pain on deep inspiration were observed with O_3 exposure but not with clean air. Airway reactivity to methacholine more than doubled following O_3 exposure.	Prolonged exposure to 0.12 ppm O_3 results in a marked increase in airway reactivity to methacholine and progressive changes in respiratory function and symptoms.	Folinsbee et al. (1988)
0 686	0.00 0.35	1 hr, CE (40 L/min)	18 females 19-28 yr old	Post-ozone exposure FVC = -14%; FEV_1 = -22%; FEF_{25-75}% = -32%; small residual effects were present 18 hr later, FVC = -3%; FEV_1 = -4%. Airway responsiveness to methacholine increased after ozone exposure.	Minor effects in spirometry following ozone exposure may persist for 18 hr.	Folinsbee and Hazucha (1988)
0 784	0.00 0.40	1 hr, CE (40 L/min)	20 males 18-35 yr old	V_T decreased 25% and f_B increased 45% with ozone exposure. FVC (-13%) and and FEV_1 (-18%) also decreased. Change in breathing pattern caused reduction in lower respiratory tract (LRT, -17%) ozone uptake.	Decreased LRT uptake was due to decreased tidal volume.	Gerrity and McDonnell (1988)
0 196 392 784	0.00 0.10 0.20 0.40	nasal, mouth and oronasal breathing @12 and 24 BPM	18 males 18-35 yr old	Removal of O_3 by the extrathoracic (nose and mouth) airways and intrathoracic airways was measured during nasal, mouth, and oronasal breathing at 12 and 24 bpm at O_3 concentrations of 0.1, 0.2, and 0.4 ppm. Overall, 39.6 ± 0.7 (SEM)% of inspired O_3 was removed by extrathoracic airways and 91.0 ± 0.5% of the remaining O_3 was removed by intrathoracic airways. Significant effects of breathing frequency, mode of breathing, and O_3 concentration were of little biological significance.	This study provides information on the distribution of inspired O_3 in the respiratory tract of humans that will (1) better define O_3 dose-response relationship and (2) contribute to the potential extrapolations of chronic pulmonary effects of O_3 from laboratory animals to humans.	Gerrity et al. (1988)

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TABLE 1. (cont'd) NEW CONTROLLED HUMAN LABORATORY AND FIELD STUDIES RELEVANT TO REVIEW OF THE 1-HR NAAQS FOR OZONE

Ozone Concentration		Exposure Duration and Activity[a]	No., Sex, and Age of Subjects	Observed Effects	Conclusions	Reference
µg/m³	ppm					
0 235 392	0.00 0.12 0.20	Competitive conditions: CE (89 L/min) for 1 hr followed by CE (150 L/min) until exhaustion @31°C and 38% rh	17 endurance cyclists 15M, 2F 24 ± 3 yr old	$\dot{V}_E$ (89 L/min), $\dot{V}O_2$ (51 ml/min/kg), work load (260 W), and work time (57 min) were similar for all exposures during submaximal exercise at 70% $\dot{V}O_2$ max; during maximal exercise, significant reductions in peak $\dot{V}_E$ (18%), $\dot{V}O_2$ (16%), tidal volume (22%), work load (8%), and ride time (30%) occurred in 0.20 ppm O_3 compared to to filtered air. Significant post-exercise decrements in FEV_1 averaged 5.6% and 21.6% in 0.12 and 0.20 ppm O_3, respectively. Respiratory symptoms were mild in 0.12 ppm O_3 but intensified to limit maximal performance in 13 subjects in 0.20 ppm O_3. Histamine airway responsiveness increased in 9 subjects after exposure to 0.20 ppm O_3 as compared with 1 subject in 0.12 ppm.	Exposure of heavily exercising endurance athletes to 0.20 ppm O_3 for 1 hr in a hot environment leads to impairment of maximal exercise performance large decrements in FEV_1 (21.6%) and FVC (19.1%), increase in airways responsiveness to histamine, and potentially limiting O_3-related respiratory symptoms. Exposure to 0.12 ppm O_3 does not limit exercise performance despite mild symptoms and small decrements in FEV_1 (5.6%) and FVC (7.6%).	Gong et al. (1986)
0 157 196 235	0.00 0.08 0.10 0.12	6.6 hr, IE (20/20) 40 L/min	21 males 18-33 yr old	Significant increases in airway responsiveness to methacholine were observed after exposure to all levels of ozone; $PD100_{AIR}/PD100_{O_3}$ were 1.56, 1.89, and 2.21 at 80, 100 and 120 ppb. $FEV_{1.0}$ decreases averaged 7, 7, and 12.3%, respectively. Small but significant increases in respiratory symptoms also occurred.	Long duration exposure to ozone levels as low as 80 ppb causes spirometry decrements and increased airway responsiveness.	Hortsman, et al. (1988,a,b)
784	0.4	30 min, CE (30 L/min)	11M, 6F healthy 18-31 yr old	No significant differences in mean decrements in FVC (4.5%), FEV_1 (5.9%), or respiratory symptoms were found between the two modes of inhalation (oral vs. nasal).	No differences in pulmonary function or respiratory symptoms were found between oral and nasal breathing of ozone.	Hynes et al. (1988)
0 784	0.0 0.4	2 hr IE (67 L/min) @15 min intervals	8 males 20-30 yr old	Increased respiratory symptoms (cough and chest tightness) and SRaw (71%), decreased FVC (14%), after 2 hr exposure to O_3 when compared to exposure in clean air. Pulmonary clearance of ^{99m}Tc-DTPA, measured 75 min after exposure, was increased in 7/8 subjects with a group mean increase from 0.59 to 1.75%/min. There was no relationship between O_3- induced change in lung function and increased radiolabeled DTPA clearance.	Ozone exposure causing decrements in lung function and increased respiratory symptoms also caused an increase in respiratory epithelial permeability, as measured by radiolabeled DTPA clearance.	Kehrl et al. (1987, 1988)

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TABLE 1. (cont'd) NEW CONTROLLED HUMAN LABORATORY AND FIELD STUDIES RELEVANT TO REVIEW OF THE 1-HR NAAQS FOR OZONE

Ozone Concentration		Exposure Duration and Activity[a]	No., Sex, and Age of Subjects	Observed Effects	Conclusions	Reference
μg/m³	ppm					
0 235 353	0.00 0.12 0.18	40 min (30 rest, 10 exercise) @33 L/min	4M, 9F healthy 14-19 yr old 8M, 8F asthmatic 11-19 yr old	No difference between air and O_3 exposure at 0.12 ppm. R_T increased after 0.18 ppm in both healthy and asthmatic subjects. FEV_1 did not change significantly.	No differences between healthy and asthmatic subjects.	Koenig et al. (1987)
0 235	0.00 0.12	1 hr, IE (33 L/min)	5M, 7F healthy 9M, 3F asthmatic 12-18 yr old	In the asthmatics, $\dot{V}50\%VC$ decreased -4.5% after air exposure, -11% after O_3 exposure, and -4% after O_3 + NO_2 (0.12 ppm) exposure. Changes in FVC and FEV_1 were similar with air or ozone exposure. No significant changes in healthy subjects.	A small but significant effect of ozone was observed in adolescent allergic asthmatics exposed to 0.12 ppm for 1 hr.	Koenig et al. (1988)
0 784	0.00 0.40	2 hr, IE (15/15) 70 L/min	11 males 18-35 yr old	FEV_1 decreased 960 ml. Post-18 hr BAL revealed 8x increase in PMN, 2x increase in albumin, protein, IgG, 6x fibronectin, 2x PGE_2 and C3a. Preliminary evidence suggests increased PMNs after 6.6 hr of 0.01 ppm O_3 exposure.	Ozone causes inflammation, increased permeability and stimulation of fibrogenesis. Inflammation persists for at least 18 hr post exposure.	Koren et al. (1988a,b,c,d,)
0 784	0.00 0.40	2 hr, IE (30 L/min/m², ~53 L/min)	5F, 4M healthy 19-31 yr old 5F, 4M asthmatic 18-34 yr old	Normal subjects FVC (-9.4%) and FEV_1(-13.2%) decreased after ozone. Asthmatic responses were larger [FVC (-14.8); FEV_1(-24.0)]. Change in SRaw (corrected for air exposure) was 0.98 units in normals and 4.2 units in asthmatics. (Ratio of % SRaw increase in air to % SRaw increase with ozone was approximately 2 for both normals and asthmatics) The SRaw and FEV_1 responses were significantly larger in asthmatics than normals. Both groups had similar increases in methacholine responsiveness.	Asthmatics have larger changes in airway resistance (obstruction) than normals but not greater changes in airway responsiveness or in the restrictive (i.e., lung volume) component of ozone-induced decrement in spirometry (i.e., FVC)	Kreit et al. (1988)
0 120-140 245-260	0.00 0.06-0.07 0.12-0.13	16-28 min progressive maximum exercise (~$\dot{V}_E$ 30-120 L/min)	12M, 12F (young)	Maximum performance time was reduced for tests conducted during ozone exposure. In female subjects exposed to 0.13 ppm performance was reduced 11%. Minimal, inconsistent changes were seen in FEV_1. Increase in symptoms of irritation, cough, etc. after tests in ozone.	Brief high intensity exercise during ozone exposure may be associated with slight decrements in indices of physical performance.	Linder et al. (1988)

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TABLE 1. (cont'd) NEW CONTROLLED HUMAN LABORATORY AND FIELD STUDIES RELEVANT TO REVIEW OF THE 1-HR NAAQS FOR OZONE

Ozone Concentration		Exposure Duration and Activity[a]	No., Sex, and Age of Subjects	Observed Effects	Conclusions	Reference
μg/m³	ppm					
0 157 196 235 274 314	0.00 0.08 0.10 0.12 0.14 0.16	2 hr IE (68 L/min) @15 min intervals 32°C and 38% rh	24 males 18-33 yr old	Forced expiratory function and symptoms in the group showed no statistically significant changes after exposure to 0.08-0.14 ppm O_3; mean FEV_1 increased 1.1% and decreased 2.3% following 1 and 2 hr of exposure to 0.16 ppm O_3 respectively, without respiratory symptoms. Two individual subjects responded at 0.14 ppm O_3, and one of them also responded at 0.12 ppm O_3	Only a mild irritant response was found in a group of young subjects intermittently exercising at heavy work loads during exposure to 0.16 ppm O_3 for 2 hr. The subjects were well-conditioned and free of asthma or clinical respiratory allergies and bronchial reactivity, possibly accounting for the observations.	Linn et al. (1986)
0 353	0.00 0.18	2 hr, IE (35 L/min/m²)	5M, 7F responders 19-40 yr old 8M, 5F non-responders 18-34 yr old	Responders (R) and non-responders (NR) were selected after ozone exposure of 59 subjects in spring 1986. R had more atopic and asthmatic subjects and ΔFEV_1 averaged -12.4%. NR were all normal and had no change in FEV_1. After summer ozone session, R experienced smaller changes in FEV_1. Reduced response persisted for several months but responsiveness returned in spring 1987. NR remained non-responsive throughout the study.	Frequent ambient ozone exposure may result in persistent reduction in ozone responsiveness of ozone-sensitive subjects.	Linn et al. (1988) Avol et al. (1988) Hackney et al. (1988) Hackney and Linn (1988)
0 353	0.00 0.18	2 hr IE (64 L/min) @15 min intervals	26 males with allergic rhinitis 18-30 yr old	Increased ($p < 0.01$) respiratory symptoms (cough, shortness of breath, and pain upon deep inspiration) and SRaw, decreased FVC, FEV_1, and $FEF_{25-75\%}$, after 2 hr exposure to O_3 when compared to exposure in clean air (CA). Airway reactivity to histamine (PC_{50}) also increased ($p < 0.01$) following O_3. After 60 min recovery in CA, significant decrements in lung function and increased symptoms were still present; some of these persisted for as long as 165 min after exposure. There were no differences in FRC, V_T, f, or V_E during exposure or recovery. Correlation coefficients between baseline PC_{50} and lung function/symptoms were not significant.	Allergic rhinitis subjects without a history of asthma-like symptoms were not more reactive to histamine than subjects without rhinitis and had similar responses to O_3 with the exception of a modest increase in bronchoconstriction. Baseline airway reactivity to histamine in this group was not associated with the magnitude of responses to O_3, as measured by lung function and respiratory symptoms.	McDonnell et al. (1987)

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TABLE 1. (cont'd) NEW CONTROLLED HUMAN LABORATORY AND FIELD STUDIES RELEVANT TO REVIEW OF THE 1-HR NAAQS FOR OZONE

Ozone Concentration $\mu g/m^3$	Ozone Concentration ppm	Exposure Duration and Activity[a]	No., Sex, and Age of Subjects	Observed Effects	Conclusions	Reference
0 392 588	0.0 0.2 0.3	1 hr (mouthpiece) IE (29 L/min for M, 23 L/min for F)	9M, 10F 55-74 yr old	R_T increased 13% in F subjects at 0.3 ppm ($p < 0.027$); no significant changes in M; no significant changes in symptoms	Older, healthy subjects are no more susceptible to O_3 than are healthy adolescents	Reisenauer et al. (1988)
0 235 353 470	0.00 0.12 0.18 0.24	1 hr (mouthpiece) CE (86.6 L/min) 30-min warm-up + 30-min endurance 23-26°C and 45-60% rh	10 male endurance athletes 19-29 yr old	All subjects completed the filtered air exposure while there was a significant increase in the inability of subjects to complete the competitive simulations with increasing O_3 O_3 concentration; 1,5 ($p < 0.10$), and 7 ($p < 0.05$) subjects did not complete the 0.12 0.18, and 0.24 ppm exposure, respectively. Significant decreases ($p < 0.05$) were observed following the 0.18 and 0.24 ppm O_3 exposures, respectively, in FVC (7.8 ad 9.9%) and FEV_1 (5.8 and 10.5%). No significant O_3 effect was observed for exercise respiratory metabolism or ventilatory patterns. The number of respiratory symptoms, however, increased significantly following the 0.18 and 0.24 ppm O_3 exposures.	This study demonstrates that significant impairment of exercise performance and pulmonary function occurs along with increased respiratory symptoms following exposure of well-trained endurance athletes to O_3 concentrations ≥ 0.18 ppm while engaged in 1 hr exercise protocol simulating competition.	Schelegle and Adams (1986)
0 784 1176	0.0 0.4 0.6	2 hr IE (83W for women, 100W for men) @15 min intervals 71.5°C, 55% rh	10 adults 3F, 7M 23-41 yr old	Increased airway reactivity to methacholine (MCh) at 0.4 ppm ($p < 0.025$) and 0.6 ppm ($p > 0.01$). Increased neutrophils in BAL of O_3-exposed subjects, particularly those with increased MCh airway reactivity Increased prostaglandin E_2, $F_2\alpha$ and thromboxane B_2 in lavage fluid 3 hr after exposure to O_3.	Ozone-induced airway reactivity to methacholine is associated with neutrophil influx into the airways and with changes in cyclooxygenase metabolites of arachidonic acid.	Seltzer et al. (1986)

[a] Activity level: CE = continuous exercise; IE = intermittent exercise; minute ventilation ($\dot{V}_E$) given in L/min; bpm = breaths per minute; W = watts.

[b] Ozone concentration of ambient air.

Data presented by Linn et al. (1986) in a controlled human study of healthy young adults exercising intermittently at heavy work loads have added more detailed concentration-response information at low O_3 concentrations ranging from 0.08 to 0.16 ppm. The ozone responsiveness of subjects in this study falls somewhere between that of subjects studied by McDonnell et al. (1983) and of those studied by Kulle et al. (1985) under similar exposure conditions (see Table 2 on key human studies at concentrations near the current 1-hr NAAQS for ozone). These subjects were also less responsive than the group previously studied by Avol et al. (1984), who were exposed to similar concentrations of O_3 but with continuous exercise for 1 hr. Although the authors of this report could not offer a definitive explanation for differences among these studies, they pointed out that individual biological factors such as the presence of asthma or clinical respiratory allergies and bronchial reactivity in individual subjects, as well as external factors such as ambient exposure history or differences in controlled exposure conditions during the study, might contribute to differences in cohort responsiveness to O_3. It is obvious that more research is needed to define better the possible reasons for the large variations in responsiveness to O_3 in individuals and the variations in group mean responsiveness across studies.

Avol et al. (1987) presented data from a laboratory field study of healthy children (8-11 yr old) exercising continuously for 1 hr in ambient air containing a mean O_3 concentration of 0.11 ppm. The same authors (Avol et al., 1985) previously studied adolescent subjects (12-15 yr old) under a similar protocol, although the O_3 concentration and exercise level were lower in the more recent study. No significant changes in respiratory function or symptoms were found in the group, probably because of the lower doses of O_3. Regression analyses of individual data, however, suggested that individuals receiving high doses of O_3 had effects that were comparable to those found in adolescents and young adults, although no definitive comparisons could be made because of differing ambient exposure levels and large intersubject variability in responsiveness to O_3. This finding is also consistent with the controlled exposure study by McDonnell et al. (1985) indicating that the effects of O_3 on lung spirometry in children were very similar to those found in adults exposed under similar conditions, except that no significant increases in symptoms were found in children. Therefore, based on the available pulmonary function data, young children and adolescents do not appear to respond differently to O_3 than adults.

TABLE 2. KEY HUMAN STUDIES NEAR THE CURRENT 1-HR NAAQS FOR OZONE

Ozone Concentration		Measurement^{a,b} Method	Exposure Duration	Activity^c Level (V_E)	Percent Change in FEV_1^{d}	Number, Sex, and Age of Subjects	Reference^e
µg/m^3	ppm						
0 157	0.00 0.08	UV, UV	1 hr	CE (57)	+0.6 +1.7 (ns) (26.4 ± 6.9)	42 male 8 female	Avol et al. (1984)
0 157 196 235	0.00 0.08 0.10 0.12	UV, UV	2 hr	IE (68)	+1.0 +2.4 (ns) +1.7 (ns)	24 male (18-33 yr)	Linn et al. (1986)
0 157 196	0.00 0.08 0.10	UV, UV	2 hr	IE (68)	+1.0 +2.4 (ns) +1.7 (ns)	24 male (18-33 yr)	Linn et al. (1986)
0 157 196 235	0.00 0.08 0.10 0.12	CHEM, UV	1 & 2 hr of 6.6 hr study	CE (40)	-1.5 (1 hr) -1.0 (2 hr) -0.4 (ns) -1.1 (ns) -1.3 (ns) -1.3 (ns) -0.5 (ns) -2.7 (ns)	21 male (18-33 yr)	Horstman et al. (1988)
0 196	0.00 0.10	UV, UV	2 hr	IE (68)	+1.5 +1.1 (nd) range: +10 to -4	20 male (25.3 ± 4.1 yr)	Kulle et al. (1985)
0 196	0.00 0.10	CHEM, NBKI	2 hr	IE (67)	-0.3 -2.6 (ns)	10 male (18-28 yr)	Folinsbee et al. (1978)
0 216	0.00^f 0.11	UV, UV	1 hr	CE (22)	-2.7 -2.9 (ns)	33 male 33 female (8-11 yr)	Avol et al. (1987)
0 235	0.00 0.12	CHEM, UV	2 hr	IE (68)	-1.0 -4.5 $(p = 0.016)^g$ range: +7 to -16	22 male (22.3 ± 3.1 yr)	McDonnell et al. (1983)
0 235	0.00 0.12	CHEM, UV	2 hr	IE (39)	-0.5 -3.4 $(p = 0.03)$ range: +5 to -22	23 male (8-11 yr)	McDonnell et al. (1985)
0 235	0.00 0.12	CHEM, UV	1 & 2 hr of 6.6 hr study	CE (40)	-0.2 (1 hr) -1.2 (2 hr) -2.6 (ns) -3.8 (ns)	10 male (18-33 yr)	Folinsbee et al. (1988)
0 235	0.00 0.12	UV	1 hr (mouthpiece)	R	-1.1 0.0 (ns)	4 male 6 female (13-18 yr)	Koenig et al. (1985)
0 235 353	0.00 0.12 0.18	UV	40 min (mouthpiece)	IE (33) 30 min R + 10 min exercise	-1.0 +1.7 (ns) -0.3 (ns)	5 male 7 females (11-19 yr)	Koenig et al. (1987)

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TABLE 2. (cont'd) KEY HUMAN STUDIES NEAR THE CURRENT 1-HR NAAQS FOR OZONE

Ozone Concentration µg/m^3	Ozone Concentration ppm	Measurement^{a,b} Method	Exposure Duration	Activity^c Level ($\dot{V}_E$)	Percent Change in FEV$_1^d$	Number, Sex, and Age of Subjects	Reference^e
0 235	0.00 0.12	UV	1 hr (mouthpiece)	IE (33)	-2.4 -0.6 (ns)	5 male 8 females (12-17 yr)	Koenig et al. (1988)
0 235	0.00 0.12	UV, UV	1 hr (mouthpiece)	CE (86)	+2.4 -1.8(ns)	10 male (19-29 yr)	Schelegle and Adams (1986)
0 235	0.00 0.12	UV, UV	1 hr	CE (89)	+4.1 -5.6 ($p < 0.02$) range: +10 to -29	15 male 2 female (24 ± 3 yr)	Gong et al. (1986)
0 235 274	0.00 0.12 0.14	UV, UV	2 hr	IE (68)	+1.0 +2.8 (ns) +1.6 (ns)	24 male (18-33 yr)	Linn et al. (1986)
0 274	0.00 0.14^f	UV, UV	1 hr	CE (31)	-0.5 -4.2 ($p < 0.01$)	46 male 13 female (12-15 yr)	Avol et al. (1985)
0 294	0.00 0.15^f	UV, UV	1 hr	CE(53)	+0.6 -5.3 ($p < 0.05$)	42 male 8 female (26.4 ± 6.9 yr)	Avol et al. (1984)
0 294	0.00 0.15	UV, UV	2 hr	IE (68)	+1.5 -0.5 (nd) range: +3 to -9	20 male (25.3 ± 4.1 yr)	Kulle et al. (1985)
0 294	0.00 0.15	UV, UV	1 hr (mouthpiece)	CE (55)	+0.6 -4.5 (ns) range: +3.5 to -30.6	10 female (22.9 ± 2.5 yr)	Gibbons and Adams (1984)
0 314	0.00 0.16	UV, UV	1 hr	CE (57)	+0.6 -6.1 ($p < 0.05$)	42 male 8 female (26.4 ± 6.9 yr)	Avol et al. (1984)
0 314	0.00 0.16	UV, UV	2 hr	IE (68)	+1.0 -2.3 ($p < 0.05$) range: +8.9 to -35.8	24 male (18-33 yr)	Linn et al. (1986)
0 314	0.00 0.16^f	UV, NBKI	1 hr	CE (38)	-0.1 -0.8 (ns)	27 male 21 female (28 ± 8 yr)	Linn et al. (1983); Avol et al. (1983)
0 333	0.00 0.17^f	UV, NBKI	1 hr	CE (42)	-0.4 -3.4 ($p < 0.006$)	45 male 15 female (30 ± 11 yr)	Linn et al. (1983); Avol et al. (1983)
0 333	0.00 0.17^f	UV, NBKI	2 hr	IE (2XR)	+0.6 -2.1 ($p < 0.05$)	14 male 20 female (29 ± 8 yr)	Linn et al. (1980, 1983)

(continued on the following page)

TABLE 2. (cont'd) KEY HUMAN STUDIES NEAR THE CURRENT 1-HR NAAQS FOR OZONE

Ozone Concentration		Measurement[a,b] Method	Exposure Duration	Activity[c] Level ($\dot{V}_E$)	Percent Change in FEV_1[d]	Number, Sex, and Age of Subjects	Reference[e]
μg/m³	ppm						
0 353	0.00 0.18	CHEM, UV	2 hr	IE (65)	-1.0 -6.2 ($p = 0.008$) range: 0 to -23	20 male (23.3 ± 2.8 yr)	McDonnell et al. (1983)
0 353	0.00 0.18	UV, UV	1 hr (mouthpiece)	CE (86)	+2.4 -5.8 ($p < 0.05$)	10 male (19-29 yr)	Schelegle and Adams (1986)
0 392	0.0 0.2	UV, UV	2 hr	IE (68)	+1.5 -3.1 (nd) range: +3 to -16	20 male (25.3 ± 4.1 yr)	Kulle et al. (1985)
0 392	0.0 0.2	UV, UV	2 hr	IE (30 for male, 18 for female subjects	+0.3 -3.1 (ns) range: +6.0 to -16.6	8 male 13 female (18-31 yr)	Gliner et al. (1983)
0 392	0.0 0.2	UV, UV	1 hr	CE (90)	+4.1 -21.6 ($p < 0.001$) range: +10 to -46	15 male 2 female (24 ± 3 yr)	Gong et al. (1986)
0 392	0.0 0.2	UV, UV	1 hr (mouthpiece)	CE (77.5)	+1.7 -6.0 ($p < 0.05$)	10 male (24 ± 4 yr)	Adams and Schelegle (1983)
0 392	0.0 0.2	UV, UV	75 min (mouthpiece)	CE (61.8)	-4.8 (ns)	8 male (22-46 yr)	Adams et al. (1981)
0 392	0.0 0.2	UV, UV	1 hr (mouthpiece)	CE (46)	-1.5 -8.0 (ns)	6 female (22-29 yr)	Lauritzen and Adams (1985)
0 412	0.00 0.21	UV, UV	1 hr	CE (89)	+1.9 -14.8 ($p < 0.05$)	6 male 1 female (18-27 yr)	Folinsbee et al. (1984)
0 470	0.00 0.24	CHEM, UV	2 hr	IE (65)	-1.0 -14.5 ($p < 0.005$) range: -1 to -36	20 male (22.9 ± 2.9 yr)	McDonnell et al. (1983)
0 470	0.00 0.24	UV, UV	1 hr	CE (60)	+0.6 -19.1 ($p < 0.05$)	42 male 8 female (26.4 ± 6.9 yr)	Avol et al. (1984)
0 470	0.00 0.24	UV, UV	1 hr (mouthpiece)	CE (86)	+2.4 -10.5 ($p < 0.05$)	10 male (19-29 yr)	Schelegle and Adams (1986)
0 490	0.00 0.25	UV, UV	2 hr	IE (68)	+1.5 -6.4 (nd) range: +1 to -36	20 male (25.3 ± 4.1 yr)	Kulle et al. (1985)

[a] Measurement method: CHEM = gas phase chemiluminescence; UV = ultraviolet photometry.

[b] Calibration method: NBKI = neutral buffered potassium iodide; UV = ultraviolet photometry.

[c] Minute ventilation reported in L/min or as a multiple of resting ventilation: IE = intermittent exercise; CE = continuous exercise.

[d] Pre to post difference (percent) in the group mean; statistical significance based on difference between O_3 and filtered air (0.0 ppm O_3) exposures: ns = not significant; nd = not determined.

[e] See U.S. Environmental Protection Agency (1986).

[f] Measured in ambient air (mobile laboratory).

[g] "Suggested" significance based on Bonferroni inequality correction ($p < 0.006$).

A series of papers have appeared in the past two years describing the effects of ozone on subjects greater than 50 years of age (Bedi et al., 1988; Bedi and Horvath, 1987; Drechsler-Parks et al., 1987, 1988; Reisenauer et al., 1988) (see Table 1).

Bedi and Horvath (1987) described the decrease in pulmonary function response in a single subject studied at age 32 and again at age 40. The major importance of this study is that it demonstrated a decline in response of considerable magnitude (ΔFEV_1 of -25% decreased to -5% over 8 years) that was observed longitudinally. This lends credence to the results of the cross-sectional studies indicating a decreased response in older subjects.

Drechsler-Parks et al. (1987) compared a group of older (age 51-76) subjects exposed to 0.45 ppm ozone with a group of young adults studied under the same protocol (2 hr intermittent exercise at 25 L/min). The older subjects had substantially smaller changes in function than the younger subjects, both male and female. FVC changes in the older subjects averaged -5.3% and, in the young adults -14.1%. Similar differences were observed for other functional measurements. Similar data for ozone exposure are reported in a second paper by Drechsler-Parks et al. (1988).

Bedi et al. (1988) reported the results of a study in which older subjects were exposed to this same ozone concentration (0.45 ppm) on three separate occasions. The responses were not reproducible from one exposure to the next. The group average did not change appreciably between exposure series indicating that even though the older subjects have more variable responses they are less responsive to ozone, as a group, than younger subjects.

Reisenauer et al. (1988) also studied a group of older subjects, age 55-74 years. These ozone exposures were conducted at 0.2 and 0.3 ppm ozone using a light intermittent exercise regime. There were no significant changes in $FEV_{1.0}$. For the 0.3 ppm exposures, however, the female subjects (n=10) had a slight rise (13%) in total respiratory resistance (R_T) that was statistically significant.

The implication of these differences in responsiveness to ozone in older subjects is unclear. Only standard spirometry tests have been used to evaluate responses. It is not known if changes in airway resistance or airway responsiveness to methacholine or histamine are similarly attenuated in older subjects. The possibility of inflammatory responses has not been studied in these older subjects.

Four publications (Eschenbacher et al., 1988; Kreit et al., 1988; Koenig et al., 1988; Koenig et al., 1987) on the effects of ozone on asthmatics have appeared recently (see Table 1). Also of interest is a recent study of subjects with allergic rhinitis (McDonnell et al., 1987).

Kreit et al. (1988) studied nine asthmatics exposed to 0.4 ppm O_3 for 2 hr while performing intermittent exercise with a ventilation of about 53 L/min. All subjects had a history of physician diagnosed asthma and were sensitive to methacholine. Medications were withheld for at least 12 hr prior to exposure. Nine nonasthmatic subjects were also studied under the same protocol. Both groups of subjects had significant decreases in FVC, FEV_1, FEV_1,/FVC, FEF_{25-75}, and IC after ozone exposure. The changes in FEV_1, FEV_1/FVC, and FEF_{25-75} were more negative in the asthmatics than in the normals (e.g., Δ% FEV_1 was -13.4% in normals and -23.1% in asthmatics). SRaw was not significantly increased in normals but was in asthmatics after ozone exposure. A significant increase in SRaw also occurred after air exposure in the asthmatics. The change in SRaw after ozone was more than twice that after exercise in air (ΔSRaw-air = +3.82; ΔSRaw-ozone = +8.02 $cmH_2O \cdot \ell^{-1} \cdot s^{-1}$). Both groups experienced a similar relative decrease in methacholine responsiveness after ozone exposure. It is important to note that these subjects underwent methacholine challenge both 90 min before and 90 min after exposure.

It is not clear to what extent the pre- and post-exposure challenge may have confounded the results, particularly since the nonasthmatics received a substantially larger dose of methacholine than the asthmatics. Normal subjects appeared to have a depressed FEF_{25-75} prior to exposure (~12% decrease after methacholine challenge). There were no differences in ozone-induced symptom responses between normals and asthmatics.

A second report of this study (Eschenbacher et al., 1988) additionally included a description of the effects of indomethacin pretreatment in ozone-exposed normal subjects. The data for asthmatics were those reported by Kreit et al. (1988). Indomethacin pretreatment in normals caused a marked decrease in ozone-induced spirometry changes ($\Delta FEV_1 - O_3$ = -21.5%; $\Delta FEV_1 - O_3$ + indomethacin = -10.6%). However, there was also a surprising, but substantial, placebo effect suggesting a possible behavioral component in ozone response. Indomethacin, an inhibitor of cyclooxygenase pathways of arachidonic acid metabolism, had no effect on the increase in airway responsiveness caused by ozone. Indomethacin appears to primarily block the "restrictive" (i.e., decreased FVC) effect of ozone and does not alter the bronchoconstrictive or airway reactivity responses. Of additional interest was the observation that "normal" subjects in the indomethacin study had an FEV_1 decrease, after an identical protocol, which was not unlike the response of the asthmatics, thus raising the question of the normality of the subjects or the possible confounding effect of a pre-exposure methacholine challenge.

The responses of adolescent asthmatics to 0.12 ppm and 0.18 ppm O_3 were tested by Koenig et al. (1987). The mouthpiece exposure sequence consisted of 30 min rest followed by 10 min exercise ($\dot{V}_E$ = 33 L/min). In addition to the 10 asthmatics, 10 healthy adolescents were also studied. There was a significant increase in total respiratory resistance (forced oscillation method) in both normals and asthmatics exposed to 0.18 ppm O_3. There were no significant changes in FEV_1 in either subject group. At 0.12 ppm O_3, there were no significant differences that could be attributed to ozone in either asthmatics or normals.

Koenig et al. (1988) have also studied adolescent asthmatics (n=10) and healthy adolescents (n=10) exposed to either air, 0.12 ppm O_3, 0.3 ppm NO_2, or the combination of O_3 plus NO_2. The mouthpiece exposures lasted 60 min and included two 15 min exercise periods during which ventilation averaged about 35 L/min. Medications were discontinued at least 4 hr prior to exposure. In the asthmatics, an 11% decrease in $FEF_{50\%}$ was observed after 0.12 ppm ozone exposure. One of the subjects had an exceptionally large decrease in $FEF_{50\%}$ of -60%, which occurred approximately 20 min after the end of exposure. This same subject did not have a large change in $FEF_{50\%}$ when exposed to O_3 plus NO_2, suggesting that the response of this individual to ozone may have been anomalous. There were no other responses attributed to ozone in this study, either in normal or asthmatic subjects. The authors tentatively suggested that adolescent asthmatics may be slightly more responsive to these low levels of ozone. However, replication of these observations will be required before this suggestion can be substantiated.

McDonnell et al. (1987) studied 26 subjects with allergic rhinitis to determine if the presence of allergies was a predisposing factor for ozone sensitivity. These allergic subjects had airway responses to histamine that were similar to a comparable group of non-allergic subjects. Exposure to 0.18 ppm O_3 for 2 hr with heavy intermittent exercise caused increased responsiveness to histamine and a decrease in several spirometric variables. The only apparent difference between the allergic subjects and previously exposed non-allergic subjects was a significant increase in airway resistance in the allergic subjects. It appears that both allergic and asthmatic subjects have a greater rise in airway resistance after ozone exposure than do normal subjects. The relative order of airway responsiveness to ozone is normal < allergic < asthmatic.

Between September 1987 and October 1988, a series of reports have been presented or published concerning a study of apparent seasonal variation in ozone responsiveness in residents of Los Angeles (Avol et al., 1988; Hackney and Linn, 1988; Hackney et al., 1988; Linn et al., 1988) (see Table 1). The definitive report of this study is the journal publication by Linn et al. (1988). From a large number of subjects tested for ozone responsiveness, 12 responsive and 13 nonresponsive subjects were selected to participate in further testing. Characteristics of the subjects are presented below:

	Gender	Age	Health Status	Mean ΔFEV_1
Nonresponders	8M/5F	5 >30	All Normal	+1%
Responders	5M/7F	2 >30	4 Normal, 6 Atopic 2 Asthmatic	-12.4%

In all tests, subjects were exposed to 0.18 ppm ozone during two hours of intermittent heavy exercise (ventilation = 35 $l \cdot min^{-1} \cdot m^2$-BSA) at 35°C and 35% RH. These 25 subjects participated in two more pairs of exposure to ozone and clean air. The initial tests were conducted in late spring (1986) and the followup tests occurred in late summer/early fall (1986) and again in winter (early 1987). A subsequent followup test with a smaller number of subjects (17 of the 25) occurred in spring (1987). The differences between responsive and nonresponsive subjects, which were of course significant at the time of the first test, were no longer significant at the first two followup studies in late summer and winter. This suggested the possibility that ambient oxidant exposure during the summer months produced an "adaptation" response which persisted for several months. This suggestion was further strengthened when a reduced number of subjects were exposed to ozone again, one year later. At this time, the responsive subjects appeared to regain their sensitivity to ozone exposure. The mean absolute changes in FEV_1 for the four exposures in the responsive subjects were -385, -17, +16, -347 ml respectively for the spring, fall, winter, and spring tests respectively. Corresponding changes for the nonresponders were +28, +90, +34, +81 ml. Because the experimental design was not optimal, these results need to viewed with caution and, as the authors state, "it is not clear that these results can be generalized." Nevertheless, these findings clearly suggest that results of experimental ozone exposures of residents of high oxidant areas must be viewed with caution if frequent ambient exposure was a possibility during the period of experimental exposure.

Additional information presented by Hackney et al. (1988) indicated that 8 of the 12 responders were reactive to methacholine and had a history of respiratory allergies. In addition, 10 of the 12 responders had a history of some symptomatic complaints when exposed to "smog". The authors suggested that allergy or atopy may be a risk factor for excess response to ozone although other studies have indicated that increased airway reactivity is not predictive of ozone responsiveness. They further speculated that nonresponders could be at increased risk for chronic health effects of cumulative ambient ozone exposure since they would be less likely to avoid such exposures because of their lack of symptomatic complaints.

Controlled human exposure studies reviewed in the EPA criteria document have suggested that some impairment of exercise performance may be associated with O_3 exposure. Subjective statements made by individuals engaged in these controlled studies indicate that the perception of pain occurring with deep breathing may be an important factor that limits performance of continuous heavy exercise at O_3 concentrations $\geq$0.18 ppm. Studies by Gong et al. (1986) and by Schelegle and Adams (1986) substantiate these earlier findings while a third study by Linder et al. (1988) suggests that small decrements in maximal exercise performance may occur at O_3 concentrations <0.18 ppm (see Table 1).

Gong et al. (1986) found that maximal performance tested after exposure of endurance athletes continuously exercising at heavy work loads ($\dot{V}_E$ = 89 L/min) for 1 hr in a hot environment was impaired in 0.20 ppm O_3. This level of O_3 exposure also reduced pulmonary function and enhanced respiratory symptoms and airway responsiveness to histamine. Maximal performance was not impaired after exposure in 0.12 ppm O_3, despite small but significant group mean decrements (5.6 percent) in FEV_1. Similarly, Schelegle and Adams (1986) found that exercise performance, as determined by completion of the exposure protocol, was impaired following exposure of endurance athletes who were continuously exercising at heavy work loads ($\dot{V}_E$ = 87 L/min) for 1 hr at O_3 concentrations $\geq$0.18 ppm but not at 0.12 ppm. Significant decrements in pulmonary function and increased respiratory symptoms also occurred at $\geq$0.18 ppm O_3.

The effect of ozone inhalation on performance of maximum exercise tests was also studied by a group of Swiss investigators (Linder et al., 1988). [A translation of this paper is available]. Twenty-four subjects (12M, 12F) were studied while performing maximal incremental exercise tests. The maximum exposure duration was 28 minutes and minimum was 16 minutes. The tests were performed in clean air, 0.07 ppm, and 0.13 ppm in an environmental chamber (24±C; 50% rh). Small significant (t-test) increases (2%) in $FEV_{1.0}$ were observed after clean air exposure. Except for women exposed to 0.13 ppm (-1.4%), no changes in FEV_1 were observed with ozone exposure. Performance on the maximum exercise test was decreased 11% in women and 7% in men at 0.13 ppm and 5% and 4% respectively at 0.07 ppm ($p < 0.05$; t-test). During the tests conducted at 0.13 ppm, there was also a small decrease (2.5 to 5%) in anaerobic threshold, defined as the workload at which the venous lactate concentration exceeded 4 mM. It is not clear to what extent the results of the exercise performance tests may reflect behavioral responses to the odor of ozone.

There are a number of questions that may be raised about the paper by Linder et al. (1988). From the graphical presentation of the data on FEV_1, it appears that no significant changes would be detected by an appropriate statistical analysis (i.e., an analysis of variance appropriate for repeated measures, rather than multiple t-tests). The authors did not indicate whether appropriate precautions were taken to randomize or "blind" the exposures. Furthermore, no information is provided about the selection criteria for subjects. Because the effects were reported for very low exposure concentrations and brief exposure durations (maximum 28 minutes), it is important to determine if these observations can be verified since they appear to be out of line with previous studies of exercise performance during ozone exposure.

The data currently available indicate that reduction in exercise performance may occur in many well-conditioned athletes after performing continuous heavy exercise for 1 hr at O_3 concentrations $\geq$0.18 ppm. These athletes are capable of sustaining very high exercise minute ventilations (i.e., >80 L/min) for 1 hr. Any performance decrements occurring at O_3 concentrations <0.18 ppm are less certain and need to be verified. It must be noted, however, that other environmental conditions, such as increased ambient temperature and/or relative humidity, may independently affect subjective symptoms and may independently impair exercise performance. Therefore, it may be difficult to differentiate work performance effects caused by O_3 from physiological or behavioral effects caused by other conditions in the environment.

Studies utilizing longer exposure durations, particularly at lower levels of exercise, have not been previously reviewed in the EPA criteria document. Among the newer data, two studies (Folinsbee et al., 1988; Horstman et al., 1988a,b) address the effects of ozone exposures for durations >2 hr (see Table 1). The first of these studies was designed to determine the effects of prolonged exposure to the present level of the 1-hr NAAQS for O_3 (0.12 ppm) on 10 young adult subjects that are representative of individuals who spend most of the day outdoors exercising at moderate intensities (e.g., adults performing heavy labor). Subjects were exposed to either 0.0 or 0.12 ppm ozone for a total of 6.6 hr. During the exposure, the subjects exercised for six periods of 50 min each; each exercise period was followed by 10 min of spirometry testing and rest. An additional 35 min for lunch was interposed between the third and fourth exercise period. The ventilation during the exercise averaged about 41.5 L/min and heart rate ranged from 108 to 124 beats/min.

Prolonged exposure to 0.12 ppm O_3 resulted in progressively larger changes in respiratory function and symptoms with time. By the end of 6.6 hr of exposure, group mean changes were as follows: FEV_1 had decreased 13.0 percent, FVC had decreased 8.3 percent, and $FEF_{25-75\%}$ had decreased 17.4 percent. On forced inspiratory tests, FIVC and $FIV_{0.5}$ were decreased 12.6 and 20.7 percent respectively. Respiratory symptoms of cough and pain on deep inspiration increased with the increasing duration of O_3 exposure. There was also a marked increase (about twofold) in airway responsiveness to methacholine following O_3 exposure. No changes were observed with clean air exposure. The changes in lung function reported at the end of exposure were similar in magnitude to those previously observed in healthy subjects performing at heavy levels of exercise ($\dot{V}_E \geq 60$ L/min) in much higher ozone concentrations (>0.2 ppm) for shorter durations (i.e., ≤ 2 hr).

The need for additional concentration-response information led to a subsequent study using the same ozone exposure protocol. Twenty subjects were exposed for 6.6 hr to four ozone concentrations (0.0, 0.08, 0.10, and 0.12 ppm) in random order. The results of these two studies were reported, in part, at the 1988 U.S.-Dutch symposium (Horstman et al., 1988a) and at the 1988 Annual APCA Meeting (Horstman et al., 1988b). The ventilation in this series was slightly lower than in the first study, averaging 38.9 L/min. The $FEV_{1.0}$ decreased by 7, 7, and 12.3% at 0.08, 0.10, and 0.12 ppm respectively. The airway resistance response to methacholine was increased by factors of 1.56, 1.89, and 2.21 respectively. There was also a significant increase in the symptom of pain upon deep breath, a typical symptom of acute ozone exposure. A complete report of this study is in preparation.

The study by Folinsbee et al. (1988) is the first clinical study to demonstrate increased airway reactivity to inhaled bronchoconstrictors in subjects exposed to low O_3 concentrations for prolonged periods of time. Other studies reported in the recent literature have identified these effects in humans exposed to O_3 for shorter durations (see Table 1). The study by McDonnell et al. (1987) described an increase in airway reactivity to histamine in 26 healthy subjects with allergic rhinitis who were exposed to 0.18 ppm O_3 for 2 hr while undergoing heavy ($\dot{V}_E$ = 64 L/min) intermittent exercise. Seltzer et al. (1986), in a study of 10 healthy individuals exposed for 2 hr to air and to either 0.4 or 0.6 ppm O_3 while undergoing moderate intermittent exercise, observed an increase in the number of neutrophils in bronchoalveolar lavage fluid 3 hr after O_3 exposure. Furthermore, they observed an increase in airway reactivity to methacholine following O_3 exposure and their data were suggestive of an association between the degree of inflammation and the increase in airway reactivity.

A new series of reports by Koren et al. (1988a,b,c,d) have described the inflammatory and biochemical changes in the airways consequent to ozone exposure (see Table 1). In these studies, subjects were exposed to 0.40 ppm for 2 hr while performing intermittent exercise (15 min exercise, 15 min rest) at a ventilation of 70 $L \cdot min^{-1} \cdot (35\ L \cdot min^{-1} \cdot m^2$ BSA); i.e., the same protocol as used by McDonnell et al., 1983. The main purpose of these studies was to examine cellular and biochemical responses in the airways of ozone exposed subjects. To accomplish this, bronchoalveolar lavage (BAL) was performed about 18 hr after the ozone exposure. Standard lung function tests were also performed before and after exposure. A mean decrease in FEV_1 of 960 ml after ozone exposure was reported. An eightfold increase in polymorphonuclear leukocytes (neutrophils) was observed after ozone exposure, confirming the observations of Seltzer et al. (1986). A twofold increase in protein, albumin, and IgG were indicative of increased epithelial permeability as previously suggested by the technetium DTPA clearance studies of Kehrl et al. (1987). In addition to confirmation of these previous findings Koren et al. (1988d) provided evidence of stimulation of fibrogenic processes including increases in fibronectin (6.4x), tissue factor (2.1x), Factor VII (1.8x), and urokinase plasminogen activator (3.6x). There was a twofold increase in the level of prostaglandin E_2 (PGE_2) and a similar elevation of the complement component C3a. Levels of the leukotrienes LTC_4 and LTB_4 were not affected.

Further evidence supporting the hypothesis that cyclooxygenase products of arachidonic acid metabolism (prostaglandins, thromboxane) may play a role in ozone-induced spirometry changes comes from a study by Schelegle et al. (1987). These investigators demonstrated a significant attenuation of decrements in FVC and $FEV_{1.0}$ when subjects were treated with the cyclooxygenase inhibitor, indomethacin, prior to ozone exposure. Subjects were exposed to 0.35 ppm for 1 hr of continuous exercise (60 L/min); $FEV_{1.0}$ decreased 26.3% on the no-drug day but only 10.6% after indomethacin pretreatment.

The above studies indicate that the inflammatory process caused by ozone exposure is promptly initiated (Seltzer et al., 1986) and persists for at least 18 hr (Koren et al., 1988d). The time course of this inflammatory response and the O_3 exposures necessary to initiate it, however, have not yet been fully elucidated. Furthermore, these studies demonstrate that cells and enzymes capable of causing damage to pulmonary tissues were increased and the proteins which play a role in the fibrotic and fibrinolytic processes were elevated as a result of ozone exposure. At the recent U.S./Dutch Symposium report, Koren et al. (1988b) reported that an inflammatory response, as indicated by increased levels of PMN, was also observed in BAL fluid from subjects exposed to 0.1 ppm O_3 for 6.6 hr (some protocol as Folinsbee et al., 1988). A complete report of these studies will be forthcoming.

Graham et al. (1988) showed an increase in neutrophils (PMN) in nasal lavage fluid collected from subjects exposed to 0.50 ppm for four hours at rest. There was a 3.5 fold increase in nasal PMN's immediately after exposure and this increased further (6.5 fold) by the following day (i.e., 20 hr later). This study suggests that a nasal inflammatory response may serve as a qualitative indicator of an inflammatory response in the lung.

Kehrl et al. (1987) observed an increased rate at which inhaled technetium labeled DTPA diffused from the airway and alveoli into the bloodstream in eight healthy subjects who endured heavy exercise for 2 hr in 0.4 ppm O_3. Kehrl et al. (1988) reported results from an additional 16 subjects studied in the same manner. For the combined group of 24 subjects exposed for 2 hr to 0.40 ppm ozone, the average rate of clearance of technetium labelled DTPA was 1.08%/min. This clearance rate was some 60% faster than that observed after air exposure. The average ozone-induced decrement in FVC in these subjects was -10%. This study confirms that clearance of ^{99m}Tc-DTPA is accelerated after ozone exposure and, in conjunction with the Koren et al. (1988) observations, strongly suggests that this accelerated clearance is due, in part, to an increased epithelial permeability within the lung. These changes in permeability are most likely associated with acute inflammation and could potentially allow better access of inhaled antigens and other substances to the submucosa. Studies of these endpoints at lower O_3 levels have not been completed.

These observations by Koren, Kehrl, and co-workers have raised the question of whether acute inflammation occurs following exposure to low levels of ozone for prolonged periods of time (>2 hr). Studies are now in progress to determine if these recently identified ozone effects are occurring at low O_3 concentrations (i.e., $\leq$0.12 ppm). This research will improve our understanding of the nature of inflammatory responses, including the biochemical and molecular changes in the lung, that occur in O_3-exposed subjects.

A recent series of papers by Gerrity and co-workers examining ozone uptake in the respiratory tract have important implications for modelling the health effects of ozone exposure in man and for extrapolating data from animals to man (see Table 1).

Gerrity et al. (1988) studied a group of 18 healthy young males to determine the fractional uptake of ozone by the upper respiratory tract, excluding the larynx (URT), and by the lower respiratory tract, including the larynx (LRT). In order to measure ozone concentrations during the breathing cycle, a chemiluminescent ozone analyzer was modified to increase its response time. Gas was sampled at the level of the posterior larynx from a tube inserted through the nose. Mean inspired and mean expired (alveolar) values of pharyngeal ozone concentration were used to compute the fractional uptake of ozone in the URT and LRT. The investigators studied the effects of changes in ozone concentration (0.1, 0.2, 0.4 ppm), breathing frequency (12 and 24 BPM) and mode of breathing (nasal, oral, oronasal). The differences between the various treatment conditions were small; the average URT uptake was about 40%

and average LRT uptake was about 91% (of the ozone that reached the larynx) resulting in an average total respiratory tract uptake of approximately 95%. (In other words, of the ozone entering the URT, about 40% was removed. Of the remaining 60% that reached the trachea, 91% of that ozone was removed. Total uptake is therefore (40% + (0.91 x 60%) = 95). Increased frequency of breathing caused a decreased fractional removal of ozone in both URT and LRT, presumably because of decreased residence time in the airway and increased flow rate. The lowest fractional removal of ozone in the URT occurred during nasal breathing. The differences between nasal and oral or oronasal breathing, however, were very small. The lack of significant differences between nasal and oral breathing on O_3-induced changes in lung function and respiratory symptoms was recently reported by Hynes et al. (1988), also suggesting that the mode of inhalation may not affect ozone uptake as much as previously expected.

In a second paper, Gerrity and McDonnell (1988) reported the influence of the ozone-induced change in breathing pattern on the ozone uptake efficiency. Subjects were exposed to 0.4 ppm ozone during continuous 60 minute exercise at a ventilation of about 40 L/min. At the end of the exposure, there was a 25% reduction in spontaneous tidal volume and a 45% increase in breathing frequency. Associated lung function changes included a 13% reduction in FVC and an 18% reduction in FEV_1. The change in breathing pattern was accompanied by a 9% reduction in the LRT ozone uptake efficiency (fractional LRT uptake decreased from 68% to 62%). Total ozone uptake (about 80%) was only reduced about 4% because there was a slight increase in ozone uptake in the URT. The reduction in LRT ozone uptake was correlated with the decrease in tidal volume, suggesting that an increased depth of inspiration increases the dose delivered to the LRT. The ozone uptake "efficiencies" reported in these two papers are not strictly comparable because the methods used to make the calculations of ozone uptake were different in each paper. The authors suggested that the reduction in tidal volume may act as a protective mechanism for the lower airways but, that the loss of this response with repeated exposures may permit increased ozone delivery to the lower respiratory tract.

Gerrity (1987) described a model of nasopharyngeal uptake of ozone using data from various animal species, including man. The conclusion reached in this analysis was that nasopharyngeal ozone uptake decreases with increasing flow but that there was also a considerable species variation in uptake (see Section 3.1.3.3 and Table 6).

The observations of Gerrity and co-workers have important implications for interpretation of heavy exercise studies. Increased tidal volume increased LRT ozone delivery but there may be a limit beyond which increases in tidal volume will not cause increased LRT ozone delivery. Further modeling studies will hopefully address whether such a limit exists in the physiological range of human ventilation.

Available data on respiratory tract uptake efficiency in humans appears to fit the predicted model, making it possible to develop dose-response information from the wealth of controlled human studies that have already been published. The current likelihood of making animal-to-man extrapolations based on this information and on the comparison of respiratory tract uptake of O_3 across different mammalian species is discussed in Section 3.1.3.3.

3.1.2 Epidemiological Studies

Newer studies of acute respiratory effects are available that show associations between ozone and respiratory effects. The results of many of the newer studies are directionally consistent with the findings of human controlled studies. Results of newer epidemiological studies, however, as with the older literature, continue to be mixed, some studies showing associations of ozone with respiratory effects and others showing no such associations or stronger associations with other pollutants or environmental variables. Where statistically significant associations between ozone and respiratory endpoints and measures have been reported, some of the newer studies have raised provocative questions that deserve and require further research and analysis. The newer epidemiological studies known to be in print or in press are summarized in Table 3. Only those studies are discussed that have data potentially or directly relevant to respiratory effects occurring in free-living populations as the result of acute exposures to ozone.

Bates and Sizto (1987) have reanalyzed earlier data (Bates and Sizto, 1983; Bates, 1985) and extended their analyses to more recent data (now covering 1974 and 1976-1982) for examining correlations between environmental variables and total respiratory admissions (TRA), TRA minus asthma (TRA-A), and nonrespiratory admissions (NRA), separately, for 79 acute-care hospitals in southern Ontario, Canada. Pollutant concentration data for O_3, NO_2, SO_2, COH

TABLE 3. NEW EPIDEMIOLOGIC STUDIES ON EFFECTS OF OZONE

Study Description	Pollutants/Environmental Variables	Results and Comments	References
Effects of pollutants and other environmental variables in summer Jul.-Aug.) and winter (Jan.-Feb.) on three categories of hospital admissions examined: total respiratory, total respiratory excluding asthma, and non-respiratory admissions to 79 acute-care hospitals serving ~5.9 million people in southern Ontario, Canada. Data for 1974 and 1976-1982 examined. Pollutant data collected from 17 stations along 280-mile corridor between Windsor and Peterborough.	Mean of 1-hr O_3 daily max: summer, 48.8-68.7 ppb; winter, 19.8-27.3 ppb. Range (avg. for 1974-1983) of 1-hr daily max O_3 in Aug., 1-199 ppb. O_3, NO_2, SO_2, SO_4, CoH, T, RH measured.	Significant correlations found in summer between O_3, SO_2, temp. (T) versus deviations from the mean respiratory admissions, with and without asthma for the same day of week in the same season and year. Stepwise multiple regression analysis based on each year separately indicates that $SO_4^=$ and T accounted for about 5% of the variance from the mean in respiratory or asthma admissions in summer. Testing of the 8-hr maximum O_3 statistic in place of the 1-hr O_3 statistic did not increase the correlation coefficient with respiratory admissions. (In winter asthma admissions were correlated with T only.)	Bates and Sizto (1987)
Extension of previous work on relationship between pollutants and hospital admissions; extended to include month of June for 1979 to 1985 and July and August of 1983. See Bates and Sizto (1987a) above.	1-hr O_3, SO_2, NO_2, $SO_4^=$, CoH measured 24-hr/day each 6th day; temp. also measured.	Analyses of O_3-associated hospital admissions for June 1983, in which O_3 levels were highest of all months and years analyzed, showed no excess of respiratory admissions in that month. Temperature explained less variance than $SO_4^=$ but temp. plus $SO_4^=$ accounted for about 3%; and with O_3 plus temp. and $SO_4^=$, variance was about 5.6%. Authors conclude there are reasons against attributing the association either to O_3 or to $SO_4^=$ and postulate that O_3 and $SO_4^=$ are co-pollutants or surrogates of causative factor. PM_{15} and $PM_{2.5}$ not measured; H^+ not measured. Aeroallergens not measured.	Bates and Sizto (1988)
Follow-up examination in 1980-1981 of cohorts of school children studied in six cities of U.S. Re-examination of between- and within-city results from earlier report (Ware et al., 1986). Respiratory symptom questionnaires completed by parents; spirometry done at school to obtain $FEV_{1.0}$, $FEV_{0.75}$, FVC, MMEF. Symptoms (cough, bronchitis, chest illness, wheeze, asthma) fit to multiple logistic model.	Continuous measurements (hourly values) of SO_2, NO_2, O_3, meteorological variables (18 hr/d). Three daily values of mean particle mass for: $PM_{2.5}$, PM_{15}, TSP; 1 daily value for FP (<2.5 µm) $SO_4^=$. Monthly means of each pollutant calculated from daily means.	All particle measures (TSP, $PM_{2.5}$, PM_{15} associated with substantial increases in respiratory illness reporting rates; only PM_{15} associations statistically significant. SO_2 (also correlated with particle measures) showed much weaker association with respiratory symptoms than association with particle measures. Association of NO_2 with symptoms was weak. Negative association of respiratory symptoms with O_3. Asthma and hay fever reported more frequently in "rural" (Portage, Topeka, Kingston) than in urban areas. Authors suggest role of pollens or other aero-allergens, at levels of pollutants in this study, in determining frequency of these allergic diseases.	Dockery et al. (1988)

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TABLE 3. (cont'd) NEW EPIDEMIOLOGIC STUDIES ON EFFECTS OF OZONE

Study Description	Pollutants/Environmental Variables	Results and Comments	References
Examination of effects of pollutants and other environmental variables on respiratory symptoms and PEFR in 11-month population study of asthmatics living in high-ozone area of Los Angeles County, CA (Glendora). Detailed questionnaires given at outset on medical and occupational histories and personal factors, including general activity patterns; battery of simple psychological tests also given each subject. Lung function (spirometry) and bronchodilator responses measured at outset in all subjects. Daily diaries (checked 2x/wk), mini-Wright flow meters (calibrated 2x/wk), and Nebulizer Chronolog attached to metered-dose broncho-inhaler used to record symptoms, day and night PEFR, and medication use, respectively. Symptom questionnaire given 2x/wk. Multiple regression analyses of increasingly larger number of subjects. Subsets (two groups of "responders") then analyzed separately and compared with rest of cohort.	NO_x, NO_2, SO_2, CO, THC measured; daily maximum of these pollutants less than CA standards or NAAQS. $SO_4^=$ >25 µg/m³ on 4 d; TSP >100 µg/m³ on 78% of days with data. Daily maximum 1-hr average O_3 concentrations (from continuous monitoring) = 0.01-0.11 ppm on 102 d; 0.12-0.19 ppm on 65 d; 0.2-0.34 ppm on 60 d; and 0.35-0.38 ppm on 3 d. Aeroallergens sampled: spores, pollens, grasses, molds, miscellaneous debris; all generally low except for group of common molds (rusts, smuts, mushrooms) present in thousands/m² on sampler.	Eight of 91 subjects completing study (of 109 recruited) showed no variability in asthma status during the 230-day study. Respiratory status of final study population (n=83) as a whole not related, either clinically or statistically, to maximum 1-hr average O_3 from <0.12-0.38 ppm. Subset analyses showed association of O_3 with symptoms and with day and night PEFR in subjects in top quartile for respiratory measures. This association did not follow a consistent relationship with ambient air concentrations of of O_3. $\dot{V}_E$ levels during outdoor time not estimated. Outcomes not related, however, to time spent outdoors versus indoors or to outdoor time on "clean" versus "smoggy" days. Subsets ("responders") differed from rest of cohort mainly in scores (Asthma Symptom Checklist) on factors representing fatigue, hyperventilation, rapid breathing. Aeroallergens from trees showed significant (and clinically relevant) relationships to respiratory variables.	Gong (1987)
Review and analysis that evaluates consistency of pulmonary/respiratory function results among 5 epidemiologic studies and compares results of 4/5 with data from controlled (chamber) studies as modeled by Hazucha (Hazucha, 1987; U.S. EPA, 1986). Studies included panel study of school children, two summer day camp studies, one residential summer camp study (Kinney, 1986; Lippmann et al., 1983, and Lippmann and Lioy, 1985; Bock et al., 1985, and Lioy et al., 1985; Spengler et al., 1985, and Ozkaynak et al., 1985). These studies were of children and/or adolescents (ages 7-16).	See individual references for pollutants and other environmental variables measured.	Results of 4 studies above have been documented in the 1986 criteria document or in this summary (see text and this table for Kinney, 1986). Transformation (assuming linearity) of data from Hazucha's quadratic model of controlled data; comparison of transformed coefficients from controlled study data with coefficients reported in the epidemiologic studies. Coefficients of pulmonary function decrements in controlled studies lower than those reported in epidemiologic studies. Authors postulate cumulative effects over multihour exposures known or thought to occur among cohorts of these 4 epidemiologic studies.	Kinney et al. (1988)
See Bock et al. (1985) and Lioy et al. (1985) summaries in Ch. 11 of criteria document (U.S. EPA, 1986); present citation records hypothesis resulting from reanalysis of data reported in the above two references.	See Bock et al. (1985) and Lioy et al. (1985) in U.S. EPA (1986)	Persistence of effects of acute O_3 exposures on PEFR reported earlier now hypothesized to be effects of cumulative daily O_3 on PEFR rather than persistence from one day to next (or more).	Lioy and Dyba (1988)

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TABLE 3. (cont'd) NEW EPIDEMIOLOGIC STUDIES ON EFFECTS OF OZONE

Study Description	Pollutants/Environmental Variables	Results and Comments	References
Effects of pollutants and other environmental variables on symptoms and lung function were examined in children attending a summer camp at Lake Couchiching (LC), about 100 km N of Toronto, Ontario. LC study was 6/30-7/8/83; cohort was n = 52, 23 nonasthmatic (11 males, 12 females) and 29 asthmatics (16 males, 13 females), avg. age of 12.1 yr. Symptom questionnaire and function tests were given twice daily to each child between 7:30-9:30 a.m. and 4:30-6:30 p.m. Children's activity levels not estimated.	Hourly O_3 ranged from ~10 ppb to ~110 ppb. SO_2, NO_x, O_3, $SO_4^=$, H_2SO_4, pH, PM_{10}, $PM_{2.5}$, RH, T, barometric pressure, wind speed and direction.	Strongest association between lung function and environmental variables was in nonasthmatics, with FVC decrements significantly correlated ($P < 0.01$) with lagged avg. $SO_4^=$, $PM_{2.5}$, and T. Unlagged PEF significantly correlated with 1-hr O_3. Significant association of T with all lung indices in nonasthmatics, but not in asthmatics. Coeff. of variation stable across morning and evening tests.	Raizenne et al. (1987)
(a) Effects of pollutants and other environmental variables on lung function were examined in girls attending one of three 2-wk Girl Guide camp sessions on north shore of Lake Erie. Cohort (n=104) was screened with methacholine challenge and with skin prick tests for 10 common respiratory allergens; 5 asthmatics withdrawn from the study (n = 99). Lung function tests were administered twice daily. Children's activity levels not estimated.	1-hr O_3 ranged from <10 ppb to 143 ppb; max. 1-hr O_3 >100 ppb on 14 days of total study (6 wk). For other pollutants, variables measured, see Raizenne et al. (1987), since protocol was the same as in that study.	(a) Associations between aerometric data and lung function measurements were not reported by pollutant in this reference. Aggregate analysis for full study not reported. Lung function changes reported for 5 episode days only. $FEV_{1.0}$ decrements statistically significant on 2 episode days for methacholine non-responsive subjects.	Raizenne et al. (1988)
(b) Subset of 12 girls (7 MC+, 5 MC-) studied pre- and post-exercise on 1 low pollution (control) day and 1 peak pollution day (episode, O_3 1-hr >139 ppb, $SO_4^=$ >80 µg/m³).		(b) Group mean FVC increased post-exercise in subset n = 12 by 40 ml, 71 ml in MC- and 17 ml in MC+. Pollution effect not statistically significant.	
See Raizenne et al. (1988) for protocol and related information. Present citation covers dosimetry aspect of study at Girl Guide camp on Lake Erie, summer 1986.	Continuous 1-hr O_3, SO_2, NO_2, and acid aerosols (as H_2SO_4); 1-hr O_3 range = 40-143 ppb; max. 12-hr acid particle concn. = 28 µg/m³ in one episode; FP-SO_4 = 100 µg/m³ for peak hr.	A dosimetry model for relating heart rate to ventilation and then to O_3 dose was developed from a 12-min, graded cycle ergometer test. In addition, 5 randomly selected children wore portable heart-rate monitors, providing data for use in the dosimetric model. Application of the dosimetry thus developed eliminated earlier statistical significance of effects of O_3 on PEFR.	Raizenne and Spengler (1988)

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TABLE 3. (cont'd) NEW EPIDEMIOLOGIC STUDIES ON EFFECTS OF OZONE

Study Description	Pollutants/Environmental Variables	Results and Comments	References
Reanalysis of daily diary study of student nurses working and living at schools in Los Angeles (Hammer et al., 1974). This paper reexamines the nurses' data using logistic regression models and time-series methods to account for serial correlation in symptom rates on successive days (see U.S. EPA, 1986, for details of Hammer et al., 1974).	Total oxidant, CO, SO_2; total oxidant concentrations reached episodic levels.	Association found between oxidant and cough and eye irritation, confirming part of findings of original study. Association with cough only at concentrations >>0.12 ppm. Previously reported association between oxidants and chest discomfort and headache (Hammer et al., 1974) were not confirmed in this reanalysis. Reanalysis did not address questions of quality of field work or possible effects on the outcomes of attrition in the study population. Reanalysis overcomes difficulties inherent in use of hockey-stick function applied in original analysis by Hammer et al.	Schwartz et al. (1988)
Effects of pollutants and other environmental variables on respiratory functions in 91 children (53 boys, 38 girls; ages 8-15) attending 2 to 4 wk of summer camp in NW New Jersey. Subsets were n = 37 for all 4 wk, n = 34 for first 2 wk only, n = 20 for last 2 wk only. Symptom questionnaire; FVC, $FEV_{1.0}$, MMEF by spirometry; and PEFR by mini-Wright flow meter were measured once/test day (most of days in camp) sometime between 11:00 a.m. and 6:30 p.m. All children had validated spirometric data for ≥ 7 of their 2- or 4-wk camp stay. Activity levels of the children were not estimated. Respiratory health status determined by parental questionnaire only. Children slept in screened-in shelters but otherwise were exposed to ambient air 24 hr/day.	Max. 1-hr O_3 ranged from 40 ppb to ~110 ppb, with max. 1-hr >80 ppb on 9 of 27 days of O_3 recorded. O_3, $SO_4^{=}$, H_2SO_4, PM_{15}, $PM_{2.5}$, T, humidity, wind speed and direction measured. Levels not reported for SO_2, pH, NO_3, NH_4^+.	Average regression slopes for respiratory function vs. max. 1-hr O_3 concentration reported for the full cohort, for boys and girls separately and for subsets in attendance for all 4 wk and for respective 2-wk sessions. Average regression slopes (±S.E.) were: -1.03 ± 0.24 and -1.42 ± 0.17 ml/ppb for FVC and $FEV_{1.0}$, respectively; and 6.78 ± 0.73 and -2.48 ± 0.26 ml/sec/ppb for PEFR and MMEF, respectively. Residuals from 1-hr O_3 vs. respiratory indices were calculated for no. hrs from 9:00 a.m. until function measurement; cumulative daily O_3 exposure (sum of 1-hr O_3 concns. from 9:00 a.m. until function measurement); avg. $[H^+]$ on day of test; avg. PM_{15} on day of test; T in hr preceding tets; RH in hr preceding test; and heat stress index (temp.-humidity index, THI). $PM_{2.5}$ residual not tested; lagged variables not tested. Most slopes of regression significant at $P < 0.05$ (differences from zero). Not clear if slopes for data subsets significantly different from each other (e.g., function vs. O_3 <60 ppb and function vs. O_3 <80 ppb). No formal analysis for a concentration threshold was performed.	Spektor et al. (1988a)

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TABLE 3. (cont'd) NEW EPIDEMIOLOGIC STUDIES ON EFFECTS OF OZONE

Study Description	Pollutants/Environmental Variables	Results and Comments	References
Effects of O_3 on respiratory function and symptoms examined in 30 non-smoking adults (2 of 10 females non-Caucasian) exercising almost daily outdoors (Tuxedo, NY) for 15 to 55 min (avg. ca. 30 min), July to early August, 1985. Pre- and post-exercise function measured and questionnaire answered post-exercise. Pulse rate, calibrated to $\dot{V}_E$ indoors, taken post-exercise. Exercise regimen self-selected. Dosimetry estimated and linear regressions of pulmonary function changes vs. mean exercise of O_3 concn.; and post-exercise function and O_3 concn. Persistence of effects tested by linear regressions. Subjects screened only by questionnaire; 2 with previous history of asthma but asymptomatic.	1-hr O_3 concn. range 21-124 ppb; average not given in text (>60 ppb) max. THI = 78°; max. acidic aerosol (as H_2SO_4) = 9 $\mu g/m_3$ during study. SO_2, NO_x, PM_{15}, $PM_{2.5}$, $SO_4^=$, NO_3^-, NH_4^+ and T and RH measured but not reported; correl. of O_3 concn. with O_3 dose, THI reported only; H^+, NH_4^+, and $SO_4^=$; concn. not reported Aeroallergens not measured.	Significant ($p < 0.01$) O_3-associated decrements in FVC, $FEV_{1.0}$, PEFR, FEF_{25-75}, and $FEV_{1.0}/FVC$. No persistence of effects seen. No symptoms reported by subjects. Mean decrements showed unexpected inverse relationship with calculated $\dot{V}_E$ levels, as indicated by regressing pulmonary function changes and post-exercise function against inhaled ozone during exercise. $\dot{V}_E$ ranges given but not group or subset means. Subjects not screened for atopy. Exercise done in Sterling Forest, wooded research park, on paved roads or trails.	Spektor et al. (1988b)
Study of pollutant-respiratory symptom relationships; children from Chestnut Ridge cross-sectional study of >4000 elementary school children. Subsamples selected from six schools in study area with consistently higher levels of air pollution during previous 4 yr. Subsamples (3) stratified by reported symptoms. One or more of following measures in 144 children: diaries, symptom questionnaire, spirometry. Telephone follow-up ea. 2 wk on diaries; spirometry done at school; pollutants (including O_3) measured at 1 monitor (data from 17 monitors for SO_2 generally reflected in data at single monitor). Diary panel study covered 8 months; successive PEFR spirometry studies of 9 wk each done in respective groups of the three subsamples.	Means and range of max. 1-hr values: O_3 mean = 32.4 $\mu g/m^3$; range = 0-129 $\mu g/m^3$; SO_2 mean = 51.2 $\mu g/m^3$; range - 18-176 $\mu g/m^3$; NO_2 mean = 40.5 $\mu g/m^3$; range = 12-79 $\mu g/m^3$; CoH mean = 0.38 CoH units; range = 0.1-1.3 CoH units; T mean = 1.3°F; range = -22° to +22°F.	Max. hourly SO_2; NO_2, O_3, and CoH; and min. T for each 24-hr period correlated with daily upper and lower respiratory illness, wheeze, and PEFR using multiple regression models adjusted for illness occurrence or level of PEFR on preceding day. No air pollutant strongly associated with respiratory illness or with PEFR. Exposure misclassification possible.	Vedal et al. (1987)

(coefficient of haze), and $SO_4^=$ were collected at 16 sampling stations, and O_3 and SO_2 at a 17th, in the Windsor and Peterborough areas and the 280-mile corridor in between. Correlations were examined for relationships among environmental variables and between environmental variables and three categories of hospital admissions for winter (Jan.-Feb.) and summer (Jul.-Aug.).

The authors concluded that an association exists in southern Ontario between O_3 and total respiratory hospital admissions (TRA) and TRA minus asthma in summer, but they note that these results are not in agreement with those of Richards et al. (1981), who found no associations between O_3 and admissions to children's hospitals or emergency room visits in Los Angeles, where O_3 levels are higher than those in southern Ontario. They concluded, as well, that aerosol sulfate levels [$SO_4^=$] explain the highest percentage variance in TRA from pollution in summer, but are not correlated with TRA in winter. Finally, they concluded that O_3 and $SO_4^=$ may be surrogates for one or more other species that travel with them in summer but not in winter, such as [H^+] in the fine-particle range.

In this study, Bates and Sizto (1987) specifically tested the maximal 8-hr O_3 average for correlation with TRA. The Pearson correlation coefficient was not affected by substitution of the 8-hr value in place of the mean of the hourly O_3 maxima previously used. The correlation between the 1-hr and 8-hr maxima across all monitoring stations was 0.986, but the correlation at one station tested was 0.867.

Using the same methodology, Bates and Sizto (1988) examined aerometric and hospital admissions data for June, July, and August 1983 and for June in the years 1979 through 1985, since June 1983 was observed to have ozone levels higher than those in any July or August previously examined. Analyses showed no excess respiratory admissions in June 1983. Furthermore, in years for which excess hospital admissions were observed in June (1982 and 1985), increased admissions were in the categories of "acute bronchitis" and "asthma," but not in other respiratory categories, a finding inconsistent with ozone-associated excess admissions reported earlier. The authors concluded that these findings cast doubt "on the primacy of ozone as the cause" of increased admissions, and that there are reasons against attributing excess admissions either to ozone or sulfate.

Raizenne and coworkers have reported on several aspects of studies of children in two summer camps in Ontario (Raizenne et al., 1987; 1988), one at Lake Couchiching (LC) about 100 km north of Toronto, Ontario, and one at a Girl

Guide (GG) camp on the north shore of Lake Erie. In the LC study (Raizenne et al., 1987) the strongest association between lung function and environmental variables was found in nonasthmatics, with FVC decrements correlated ($p < 0.01$) with 24-hr lag functions for average $SO_4^=$, $PM_{2.5}$, and T. The association of PEF with unlagged 1-hr O_3 was statistically significant and the average slope of the regression line was -2.7 (ml/sec/ppb). Temperature (T) was significantly associated with all lung indices in nonasthmatics but not in asthmatics. The average slope of PEF for T in nonasthmatics was -21.7, a much stronger association of PEF with T than with O_3. Coefficients of variation (CV%) were stable across the daily morning and evening tests of pulmonary function. Though asthmatics had somewhat larger CV%, no statistical differences in CV% for a.m. versus p.m. tests were seen in either group. Activity or exercise levels were not estimated, nor was amount of indoor (as on rainy days) versus outdoor activity estimated (i.e., actual exposure as well as proportion of higher versus lower exercise levels).

Raizenne et al. (1988) have recently presented preliminary data from the study of the effects of air pollution on girls aged 8 to 14 who attended one of three consecutive 2-week sessions of the Girl Guide camp on Lake Erie (June 29 through August 9, 1986). The health status of each camper participating in the study (112 of 145) was characterized by questionnaires completed by parents, by bronchial challenge (methacholine, Mch), and by skin-prick tests for atopy. The influence of air pollution episodes on lung function was examined by comparing lung function responses for each girl on episode days with mean responses on "control" days (the latter defined as days with a 1-hr ozone maximum of ≤ 90 ppb; $SO_4^= \leq 15$ μg/m^3; $H_2SO_4^= \leq 10$ μg/m^3). Additionally, lung function on the morning following an ozone episode versus the average function on control days was examined.

Maximum decrements of 3.5% and 7% for $FEV_{1.0}$ and PEF, respectively, were reported to be associated with four distinct air pollution episodes in which O_3, H^+, and $SO_4^=$ were all elevated. Only $FEV_{1.0}$ changes were statistically significant, on 2 episode days (one each in camp sessions 1 and 2). For each camp session, the mean values for FVC, $FEV_{1.0}$, and MMEF exhibited a U-shaped pattern over time; larger first-day decrements were followed by a subsequent, more gradual return to baseline. This pattern was not observed for PEF. The largest $FEV_{1.0}$ and PEF decrements were observed in Mch+ children the morning after (July 26) the highest ozone level measured (July 25) during the study. In Mch- children, however, the $FEV_{1.0}$ change was positive and the PEF change was negative, both on July 25 and July 26. In camp session three, improvement in both $FEV_{1.0}$ and PEF were noted. The authors postulated the exposure of campers in session three to a regional episode prior to their arrival in camp, with recovery occurring while at camp. No hypothesis was put forward to explain the positive $FEV_{1.0}$ change in Mch- children on the day of the highest peak ozone level and on the day following. The lack of an aggregate analysis and the presence of largely unexplained temporal trends in pulmonary function make interpretation of these study results difficult. This report of the study does not provide strong evidence for the effects of ozone or of air pollution episodes on pulmonary function.

On July 25, when the 1-hr ozone level was elevated (143 ppb), 12 subjects performed pre- and post-exercise spirometry (exercise level and resulting minute ventilation not estimated). For this subset of subjects, post-exercise FVC and $FEV_{1.0}$ were observed to increase on control day tests and to decrease on the episode day (results on the episode day were compared with the mean PFT results for all control days). The function changes did not attain statistical significance, however (Raizenne et al., 1988).

During the study of girls attending the Lake Erie residential camp, investigators (Raizenne and Spengler, 1988) examined the use of heart rate as a surrogate for pulmonary ventilation during daily activities. A dosimetric model was developed using heart-rate data from a standardized exercise test and from portable heart-rate recording devices. Individual exposure estimates were developed, based on time-activity data, and were related to changes in lung function observed in the children. For both ozone and sulfuric acid, the slopes of function (PEFR) versus pollutant did not differ from zero when the data were adjusted for dosimetry. Adjusted data for $FEV_{1.0}$ were not reported.

From a study they conducted in 1984 at a YMCA summer camp (Fairview Lake) in northwestern NJ, Spektor et al. (1988a) have reported associations between O_3 and variations in respiratory functions for 91 children attending camp for at least 2 weeks. Average slopes for the regressions between O_3 concentrations and functions were significantly negative ($p < 0.05$) for FVC, $FEV_{1.0}$, MMEF, and PEFR for all children and for boys and girls separately. Comparable data were obtained for cohort subsets (2-week campers). When data were truncated at a heat stress index (THI) of 78°F, the average slopes for girls were reduced by half for the data sets restricted to THI <78°F, eliminating significant differences in $FEV_{1.0}$ changes between girls and boys. Little or no comparable effect of a heat stress component was seen in boys. Activity levels were not estimated, so that the $\dot{V}_E$ component of the responses was not estimated for individual children or for cohort subsets.

As reported by the authors, multiple regression analyses indicated that the O_3 concentration in the hour preceding spirometry, the cumulative daily O_3 exposure during the hours between 9 a.m. and the function measurement, ambient temperature, and humidity were the most explanatory environmental variables for daily variations in function, with the 1-hr O_3 concentration having the strongest influence. The authors calculated predicted average functional decrements from the average slopes of the base data set (Table 1, Spektor et al., 1988a), assuming the exposure-response curve to be linear, of: FVC, 4.9%; FEV, 7.7%; PEFR, 17%; and MMEF, 11%; for O_3 at the current standard of 120 ppb. Of the 91 children studied, 33 (36%) had individually statistically significant $FEV_{1.0}$ responses, with an average coefficient in that subset of -2.97 ml/ppb, or about a 16% decrement--again assuming linearity--at 120 ppb O_3. The values for the 2-week subsets are generally consistent directionally with O_3 concentrations in the respective 2-week periods and the total period. Likewise, slopes for data truncated at <60 ppb and <80 ppb O_3 show general directional consistency with the O_3 concentration data except for FEF_{25-75}.

Several considerations should be noted. Ozone and temperature are highly correlated in this study, with evidence of effects of heat stress on ozone-associated decrements in function. If the respiratory effects depend nonlinearly on interactions between temperature (or THI) and ozone, this may confound interpretation of the effects of ozone. Data were truncated at 60 and 80 ppb and the conclusion was drawn that ozone-associated effects occurred at <60 ppb. A formal test for threshold would seem to be in order. The differing number of pulmonary function test days does not appear to have been adequately accounted for in the pooled analysis. The results of this apparently well-conducted study might be strengthened by additional analyses. As reported, calculated decrements at the level of the current standard should be interpreted cautiously.

Reanalyzing data from the Mendham, New Jersey, day camp study (Bock et al., 1985), Lioy et al. (1985) hypothesized that PEFR decrements associated with a 4-day ozone episode (concentrations >0.12 ppm) persisted on subsequent days. Lioy and Dyba have recently (1988) proposed, however, that a more likely explanation is that the PEFR decrements seen were the result of the total ozone dose rather than a persistence from one day to the next.

In a study by Kinney, the effects of air pollutants on lung function were measured by spirometry in children (ages 10-12, 90 male and 64 female) in Kingston and Harrisman, TN, with spirometry done at least six times, ≥ 1 week apart, from February through April 1981 (Kinney, 1986; cited in Kinney et al., 1988). Ozone and other pollutants were monitored at a single site in central Harriman. Temperature and aeroallergens were not measured. Values for FVC, $FEV_{75\%}$, MMEF, and $V_{75\%}$ were regressed (ordinary least squares model) on the 1-hr maximum O_3 concentrations and on the 24-hr-average FP and FP-sulfate concentrations. Ozone concentrations ranged from 3 to 63 ppb during the study. Concentrations of other pollutants (SO_2, NO_2, TSP, IP, RSP, and FP) were not reported. Slopes of all four lung function-ozone regressions were significantly negative. A positive mean slope of MMEF on fine particle concentrations was reported. As noted in Kinney et al. (1988), outdoor-only monitoring and lack of time-activity data compromise the specification of true exposures; and the low ozone concentrations present during the study detract from plausibility.

Vedal et al. (1987) have reported data from an 8-month panel study of symptoms and from concurrent but successive 9-week PEFR studies in asthmatic and nonasthmatic school children living in the Chestnut Ridge area of western Pennsylvania. Neither respiratory symptoms nor PEFR was strongly associated with any of the environmental variables, which included peak 1-hr ozone, NO_2, SO_2, and CoH, and daily temperature. Level of PEFR on the previous day was the strongest predictor of daily PEFR. True exposures to ozone and other pollutants were probably misspecified, since data were obtained from only one monitor for the whole area, except for SO_2, for which an average of values from 17 monitors was used; and individual exposures and activity levels were not estimated. Further, levels of ozone during this school-year study were low, ranging from 0 to 65 ppb, with a mean of 16 ppb.

Results for the 1980-1981 school year have been recently reported by Dockery et al. (1988) from an ongoing study of the effects of ambient air pollution on respiratory health in children living in six cities in the United States: Watertown, MA; Kingston-Harriman, TN; Steubenville, OH; Portage, WI; a geographically defined portion of St. Louis, MO; and Topeka, KS. Previous results showed that the reported prevalence of chronic cough, bronchitis, and chest illness increased by about a factor of two across the range of TSP and SO_2 concentrations measured in the six cities. Lung function was determined at school by spirometry and a respiratory illness and symptom questionnaire was completed by each child's parents. Pollutants measured included TSP and particles $\leq$15 μm and $\leq$2.5 μm (PM_{15} and $PM_{2.5}$), ozone, NO_2, and SO_2. The pulmonary function parameters measured were FVC, $FEV_{1.0}$, $FEV_{0.75}$, and MMEF. Five respiratory illness or symptom categories were considered: bronchitis, cough, chest illness, wheeze, and asthma.

No association was found between air pollutant levels and the pulmonary function measures, including $FEV_{0.75}$ and MMEF, which are more sensitive measures than $FEV_{1.0}$ and FVC of small airway impairment. As in previously reported results from earlier years of this study, chronic cough, bronchitis, and chest illness were positively associated with all three measures of particulate pollution--TSP, PM_{15}, and $PM_{2.5}$--but only associations with PM_{15} were statistically significant. Sulfur dioxide, which showed correlation with the particulate measures, was much more weakly associated than particles with the respiratory symptoms. The association of NO_2 with respiratory symptoms was also weak. According to the authors, the "negative associations of respiratory symptoms with ozone probably do not represent a protective effect of ozone, but rather indicate the negative correlation between ozone and other pollutants."

In this context, it is worth noting that a recent reanalysis by Schwartz et al. (1988) of the Los Angeles study of student nurses (Hammer et al., 1974) showed no association between ozone and respiratory symptoms other than cough; and the association between ozone and cough was not seen until peak 1-hr ozone concentrations were "well above the current ambient standard for ozone" (>>0.12 ppm). The reanalysis was done by logistic regression models and time-series methods; whereas a hockey-stick function was used in the original analysis.

Spektor et al. (1988b) conducted a study of the effects of ozone in ambient air on pulmonary function in 30 healthy adult nonsmokers (20 males, all Caucasian; 10 females, 2 non-Caucasian) exercising outdoors each work day (between 11:30 a.m. and 6:30 p.m., June 27-August 2, 1985, except for July 4 and 5) in Sterling Forest research park in Tuxedo, New York. A respiratory questionnaire was administered before exercise and spirometry was performed before and after exercise. The outdoor exercise regimen was selected by the subject. Following each exercise stint, the subject measured his own pulse rate. Ventilation ($\dot{V}_E$) for each exercise period was estimated from the subject-reported heart-rate data, calibrated from heart-rate data recorded from indoor treadmill exercise at a pace similar to the outdoor exercise level.

For each subject, on each exercise day, pre- and post-exercise function measurements were taken, and changes in function were determined for FVC, $FEV_{1.0}$, $(FEV_{1.0}/FVC)$, PEFR, and FEF_{25-75}. Subject-specific exposures were estimated from duration of exercise, mean O_3 concentration during the exercise period, minute ventilation, and the tidal O_3 inhaled during exercise. Pollutants and environmental variables measured were: ozone, SO_2, NO_x, ambient aerosols (PM_{15} and $PM_{2.5}$), aerosol acidity and other fine-particle ions, temperature, humidity, and wind speed and direction. Pulmonary function variables were regressed on mean O_3 concentration during exercise for each subject, as well as against the O_3 concentration during exercise on the preceding day. Interactions of other environmental variables with ozone were tested.

All pulmonary function indices showed significant ($p > 0.01$) ozone-associated decrements. No clear effects from other variables on the effects of ozone were seen. Mean decrements were reported as smaller in 10 subjects with $\dot{V}_E$ >100 L/min than those in 10 subjects with $\dot{V}_E$ of 60 to 100 L/min or those in 10 subjects with $\dot{V}_E$ <60 L/min. The decrements were reported to be about twice as large as those seen in 1- to 2-hr chamber studies in which $\dot{V}_E$ levels were comparable. No association was found between pre-exercise lung function and mean ozone concentration during exercise on the preceding day (no persistence). No symptomatic responses were reported. Analysis of lung function changes for ventilations of 50 to 80 L/min was reported by the authors to indicate that the influence of $\dot{V}_E$ on lung function decrements peaks at about 80 L/min.

This study appears to offer qualitative substantiation of the effects of ozone on respiratory function in populations engaging in continuous exercise outdoors for short periods of time (15 to ca. 60 minutes; average duration of ca. 30 minutes). In addition, it is useful for the hypotheses it generates. As with many apparently well-designed studies, however, this study raises at least as many questions as it answers. When conditions of field or epidemiologic studies begin to approximate those of controlled studies, and when data are quantitatively compared by the investigators to those obtained in controlled studies, methodologic considerations become all the more important. Thus, several points regarding this study are worth mentioning.

Methodologically, the use of heart-rate data in the absence of actual heart-rate monitors raises questions about whether (a) the pulse was taken soon enough after exercise to permit valid calculation of $\dot{V}_E$ levels: (b) whether the treadmill-exercise heart-rate data were obtained through steady-state or through incremental workloads; but, perhaps more important, (c) whether the $\dot{V}_E$ levels, especially the higher levels apparently attained in some subjects, were constant throughout the exercise period or whether they resulted from end-of-run aerobic sprints, resulting in a post-exercise heart rate higher than the prevailing rate during most of the exercise period. The latter would lead to an overestimation of $\dot{V}_E$ levels and of inhaled dose during exercise.

With regard to the statistical methods used, the estimation of effects in the most sensitive subgroups is questionable. Individual slopes are highly variable because of biological variation in pulmonary function changes, such that individuals having the largest slopes are not necessarily the most sensitive individuals. Furthermore, the observed slopes are more variable than the true slopes because of sampling variability, resulting in a bias away from zero of the average coefficient in the subgroup with large observed slopes.

Additional information would be helpful for determining the adequacy of the exposure characterization in this study. For example, it is not clear whether ozone concentrations were the same in the respective microenvironments (macadam roads versus trails); or whether one group of exercisers (runners versus walkers, for example) consistently chose one microenvironment over another. In addition, aeroallergens were not measured, but would have been a potentially useful exposure measure given the nature of the study site.

Kinney et al. (1988) recently published a critical evaluation of five epidemiological studies of the effects on lung function of acute exposures to ozone. In that review, they compared the coefficients of ozone-associated lung function declines reported in those studies with data derived from a synthesis by Hazucha of results of controlled studies. Hazucha modeled the effects of $\dot{V}_E$ in potentiating the effects of ozone on pulmonary function, using pooled data from 2-hr chamber studies of healthy young adults exercising intermittently. Kinney et al. (1988) re-expressed the data of Hazucha in units consistent with the epidemiologic study results (assuming a linear relationship between lung function decline and concentrations up to 100 ppb and using baseline functions obtained in Kinney, 1986).

The resulting coefficients were reported as being larger than those from controlled studies, especially for FVC, which was about five times the mean FVC coefficients from controlled studies. They concluded that the "effective" exposures in the epidemiologic studies were cumulative over longer periods (from 8 to 12 hr versus the 2-hr exposures used to generate the data analyzed by Hazucha).

No justification was given for the use of the linear model and the transformation of data from Hazucha (1987), who had used a quadratic model. At concentrations $\leq$100 ppb, a linear model would overestimate lung function decrements if the quadratic model is more appropriate; while at higher ozone concentrations it would underestimate lung function decline in comparison to a quadratic model. Although the range of ozone concentrations in the epidemiologic studies reviewed overlap those used in the controlled studies modeled by Hazucha, the mean concentrations in the respective epidemiologic studies from which data were used were <100 ppb (see, e.g., Bock et al., 1985; Kinney, 1986).

While asthmatics are not unequivocally more sensitive to ozone than nonasthmatics, neither have they been shown to be less sensitive (U.S. Environmental Protection Agency, 1986). Therefore, the findings of a recent epidemiologic study of asthmatics are included here. Gong (1987) studied the relationship between air quality and the respiratory status of 83 asthmatics living in a high-oxidant area of Los Angeles County. The study covered February to December 1983, but data analysis was limited to a 230-day period (April 15-November 30) because of staggered entry of subjects into the study and the high frequency of missing or incomplete data encountered in the earlier part of the study period.

Regression and correlation analyses between ozone and average symptom scores, asthma medication index (AMI), and day and night PEFR across subjects showed weak, non-significant relationships. These daily outcome variables were compared for days with maximum 1-hr-avg ozone in three ranges: <0.12 ppm; 0.12-0.19 ppm; and >0.20 ppm; "no statistical or clinical significance was detected." Individual exposures and activity patterns were not estimated in these two analyses.

Multiple regression analyses also supported the lack of a significant overall relationship between ozone (and other independent variables) and respiratory status, despite the use of lagged variables and the inclusion of other pollutants, meteorological variables, aeroallergens, and AMI. Total suspended particulates directly affected PEFR but the relationship was not consistent in the analysis. Aeroallergens showed significantly negative relationships to respiratory variables, but only the effect of trees was considered clinically relevant. Temperature and humidity showed no significant effect on the respiratory variables in this study.

Although there was no significant overall effect of ozone on respiratory variables in the 83 asthmatic subjects, multiple regression analysis of subjects whose ozone coefficients on various days were in the top quartile for dependent variables (respiratory measures) showed significant and consistent effects of ozone on day t and the previous day (t-1). Multiple regression testing of subsets for associations of symptom score or day or night PEFR on the same day's ozone and the previous day's value of the same responses showed highly significant ozone coefficients for all three respiratory measures.

The clinical significance of responses in symptom scores and day and night PEFR was evaluated for all subjects by individual regression analyses. No subject had evidence of significant worsening of symptoms attributable to ozone during the study. Adult subjects with high scores in fatigue, hyperventilation, dyspnea, congestion, and rapid breathing in the Asthma Symptom Checklist had more negative slope coefficients for ozone than subjects with low-to-moderate scores on the checklist. "Responders" (statistically identified by multiple regression analysis) scored consistently higher in the the factors representing fatigue, hyperventilation, and rapid breathing. The higher scores of these "responders," however, "were apparently not associated with differences in ambient ozone concentrations since the test scores were similar during relatively low (first test) and high (second test) ozone days. The significance of the psychological results is unclear at this time and will be the subject of further analyses" (Gong, 1987).

3.1.3 Laboratory Animal Studies

The recently published and in press reports on the animal toxicology of O_3 were evaluated according to their overall relevance to the issues of O_3 toxicology described below. A report not clearly applicable or unique in its contribution was not considered. Hence, studies that added little or no data or insight to the issues being addressed, and that corroborated or tended to duplicate the content of other studies, were eliminated in order to summarize the newer pertinent data as briefly as possible. New literature has been selected for review here that contained information on: (1) the effects of multihour exposures to O_3; (2) the potential health effects of chronic O_3 exposure; and (3) the conceptual and empirical linkages between animal and human O_3 toxicology, i.e., extrapolation. Information on a less-specific, but nevertheless important, aspect of O_3 toxicity (e.g., "adaptation") is given here as well.

3.1.3.1 Effects of Multihour Exposures--Three new studies on the effects in animals of multihour exposures to O_3 (Table 4) have been reported by researchers at the Dutch RIVM (van Bree et al., 1988; Rombout et al., 1988) and at the U.S. Environmental Protection Agency (Costa et al., 1988a). Results of these studies point to the fact that concentration (C) dominates duration of exposure (T) in eliciting a toxic response to the lung as determined by lavagable plasma protein on the lung surface. All three studies suggest that exposure C and T (as well as kill-time in the case of Dutch studies) can be modeled mathematically and clearly demonstrate the dominance of C in eliciting effects. Santrock et al. (1988) have shown in mice that products of $[18]O_3$ accumulate linearly in the lungs over at least 1 hr of exposure at 1 ppm. Although the effect of T on response is clearly C dependent, the influence of T is apparent at all levels with some indication that C and T interact in a synergistic manner in the low C-long T exposures. While further work on this last point is needed, it appears that the CxT approach only holds for a given C and cannot be applied in a general fashion.

The protein and PMN response to repeated 12 hr nocturnal exposures for up to 3 days as an analogue of an O_3 "episode" (van Bree et al., 1988) appeared to be governed by the initial exposure only. In other words, the degree of response and recovery time were unaltered by additional exposures during the 2- or 3-day period. Repeated 2-hr exposures of rats for up to 5 days (Costa et al., 1988b) resulted in adaptation or attenuation of the O_3-induced functional deficits, with sustained but not worsening protein accumulation occurring in the lavage. However, the histopathology of these animals appeared to worsen and evolve from an acute to a more chronic inflammatory pattern. Recovery or exposure points beyond 5 days were not conducted. Antioxidant levels of the lung tissues showed a slight upward trend during this period, but their role in the pattern of response is unclear.

Costa et al. (1988a) have attempted to address whether the apparent cumulative loss of lung function seen with O_3 exposure in human subjects also occurs in experimental laboratory animals. As reported in humans by Folinsbee et al. (1988), FVC fell in a linear fashion with estimated cumulative dose which incorporated ventilation, but only at lower concentrations ($\leq$0.5 ppm for

TABLE 4. NEW EXPERIMENTAL ANIMAL STUDIES ON MULTIHOUR EXPOSURES TO OZONE

Ozone Concentration		Exposure Duration and Protocol	Species	Observed Effects	Conclusions	Reference
$\mu g/m^3$	ppm					
250 500 750 1500 4000	0.13 0.26 0.38 0.77 2.0	0, 1, 2, 4, or 8 hr, 1-54 hr	Wistar rats	Concentration, duration and time of exposure affected response of lavage fluid protein levels. Duration of exposures less than half as significant as time of exposure. Concentration dominated.	The time of exposure day is important in studying oxidant toxicity. The primary determinants are concentration and time followed by duration. A quadratic polynomial could model the response.	Rombout et al. (1988)
784	0.4	12 hr; 1-3, 7 days	Wistar rats	Acute inflammation resulted from O_3 exposure as indicated by lavage fluid protein and tissue antioxidant enzymes. Exposures of 1-3 days did not alter the peak or recovery profiles of lavage fluid protein or PMNs.	Oxidant stress is evident at the lung tissue level. Effects of O_3 beyond 1 day do not appear to be cumulative. Recovery from exposure is unaltered from 1-3 days of exposure.	van Bree et al. (1988)
196 392 784 1568 2352	0.1 0.2 0.4 0.8 1.2	1-8 hr	F-344 male rats	Matrix study design showed dominance of C over T in protein responses.	A polynomial model described data and suggested CxT interaction (synergism) at decreased C and increased T. The CxT = k could only be applied at constant C.	Costa et al. (1988a,b)
980 1568	0.5 0.8	2 or 7 hr with CO_2 hyperventilation		Lung function variables showed T effects but were dominated by C. Linearity held for FVC, as seen in humans, but did not hold for other variables.	C dominates T. Functional changes do not correlate with permeability to protein. Rat model mimics human data and can be appropriately applied.	

up to 7 hr). At 0.8 ppm, the effect of T on the C response dramatically increased as was seen in their matrix studies of CxT relationships and in similar studies by van Bree et al. (1988). Hence, the impact of T is C dependent. It should be noted, however, that the apparent cumulative toxicity of O_3 may be endpoint dependent as well and that the simple loss of lung volume, FVC or FEV_1, may demonstrate such a relationship (linearity) more clearly than more interdependent measures such as DL_{CO}, N_2 washout etc.

3.1.3.2 Effects of Chronic Exposure to Ozone--The bulk of the recent reports on O_3 effects in laboratory animals have focused on the structural alterations of the distal lung associated with prolonged, repeated exposures (see Table 5). In both the adult and neonate rat (Barry et al., 1988; Grose et al., 1988; Huang et al., 1988; Gross and White, 1987) and the monkey (Tyler et al., 1988; Hyde et al., 1988), high ($\geq$0.25 ppm) ambient levels of O_3 appear to affect similarly the junctional airways of the distal bronchioles and the proximal alveoli. Shifts in cell population occur that result in more cuboidal cells interfacing the airway lumen, effectively presenting less cell surface to the air, and presumably reducing individual cell dose Barry and Crapo, 1985; Barry et al., 1985, 1988; Sherwin and Richters, 1985). Interstitial inflammation predominates over time, resulting in thickened septal areas that do not completely recover during several weeks of post-exposure clean air (Huang et al., 1988; Barr et al., 1988; Moffatt et al., 1987). In fact, alternate months of O_3 yielded no difference in ultimate 18-month pathology in monkeys exposed continually to 0.25 ppm, thereby supporting the observations of a "smoldering' persistent lesion (Tyler et al., 1988). These findings are largely consistent with the reports of enhanced collagen deposition and reduced turnover with very high ambient levels of O_3 (0.57-0.8 ppm) in monkeys (Reiser et al., 1987) and rats (Hacker et al., 1986; Pickrell et al., 1987), but appear discrepant with collagen analyses in chronically exposed rats at very O_3 concentrations (Filipowicz and McCauley, 1986; Wright et al., 1988) unless exposure is intermittent (Tyler et al., 1988).

Recently, preliminary reports from the U.S Environmental Protection Agency's chronic O_3 study (Grose et al., 1988) showed that repeated daily exposure of rats to a daily episodic profile of O_3 (22 hr, 0.06 ppm background with a 0.25 ppm peak; equivalent to a square wave that averaged 0.19 ppm over 9 hours) for 12 months resulted in small, but significant decrements in lung function that were consistent with early signs of focal fibrogenesis in

TABLE 5. CHRONIC OZONE EFFECTS IN EXPERIMENTAL ANIMALS

Ozone Concentration μg/m³	Ozone Concentration ppm	Exposure Duration and Protocol	Species	Observed Effects	Conclusions	Reference
1862	0.95	8 hr/day for 90 days	Male Sprague-Dawley rats	Inflammation in proximal acinus; decrease in terminal bronchial lumen diameter without change in volume while respiratory bronchiole volume increased 3.4x.	Respiratory bronchioles are formed from centriacinar alveolar ducts. The focal lesion induced by O_3 within the acinus appears to shift distally with respiratory bronchiolization.	Barr et al. (1988)
235 1470	0.12 0.25	12 hr/day for 6 wks	F344 rats: neonates vs. adults	Damage to proximal alveolar tissues. Shift in cell population to more, smaller, cuboidal cells. Epithelial thickness increased, interstitial macrophages doubled.	Enhanced Type I cell turnover, interstitial inflammation was dose dependent; no age related differences.	Barry et al. (1985) Barry and Crapo (1985)
490	0.25	12 hr/day for 6 weeks	Male F-344 juvenile or young adult rats	Decreased ciliated surface of Clara cells, and number of brush cells per mm^2 of terminal bronchiolar basement membrane.	Structure of the terminal bronchiolar cells is significantly altered.	Barry et al. (1988)
245 490 980	0.125 0.25 0.50	21 hr/day for 3-12 mo	F344 male rats	No increase in lung collagen or total protein content. Significant increase in ^3H protein incorporation into collagen and total protein in O_3 exposed rats.	Prolonged exposure to O_3 increases the turnover rate of lung collagen and total protein content.	Filipowicz and McCauley (1986)
118 490	0.06 0.25	0.06 ppm for 13 hr/day; slow 9 hr peak of 0.25 ppm, 5 days/wk; for 12 mo	F344 male rats	Decrements in lung volume, N_2 washout consistent with restrictive lung lesions. Antioxidant enzymes were enhanced and lavage fluid protein was elevated.	Lung lesion resulting from O_3 exposure is evident and appears to to be restrictive in nature, suggesting possible fibrogenesis.	Grose et al. (1988)
1372	0.70	20 hr/day for 28 days; post-exposure of 4-9 wks	F344 male rats	Decreased lung volumes, decreased DL_{CO} and altered airflow mechanics after exposure. 4 wk recovery allowed most parameters to return to normal. Some flow decrement remained through 9 wks. Some interstitial collagen remained after each mild inflammation.	Airflow dysfunction may be related to thickening of alveolar ductal regions. Continuous recovery postexposure was not apparent for some of the flow related variables.	Gross and White (1986)
980	0.5	20 hr/day for 52 wks; 12 wk post-exposure recovery; kills at 6 and 12 mos	F344 male rats	Increases in FRC and RV at 6 and 12 mo.; DL_{CO} decreased over same period. The 3 month recovery period resulted in reversibility of the functional lesion. Inflammation was mildly correlated with function and reversed.	Chronic O_3 exposure in rats induces a mild lesion which is reversible. As a model, it suggests little impact of O_3 on public health.	Gross and White (1987)
1568	0.8	3 days	Male Sprague-Dawley rats, 24-365 days old	Increased collagen synthesis with greatest changes occurring at >60 days of age.	Increased collagen synthesis following O_3 exposure may be age dependent.	Hacker et al. (1986)
1568	0.8 4.0	3 days, followed by 4.0 ppm for 8 hr with 60 day		Increased lung collagen content (hydroxyproline)		

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TABLE 5. (cont'd) CHRONIC OZONE EFFECTS IN EXPERIMENTAL ANIMALS

Ozone Concentration µg/m³	Ozone Concentration ppm	Exposure Duration and Protocol	Species	Observed Effects	Conclusions	Reference
294	0.15	8 hr/day for 6 or 90 days	Bonnet monkeys	Qualitative changes in secretory products in nasal epithelium caused by 0.15 ppm for 6 days; also quantitative changes: increase in stained mucosubstance after O_3 exposure for 6 days; after 90 days, there was significantly less than after 6 days; nasopharyngeal region only minimally affected and only at 6 days.	O_3 causes quantitative changes in stored secretory product in anterior nasal cavity epithelium.	Harkema et al. (1987a)
294 588	0.15 0.30	8 hr/day for 6 or 90 days	Macaque monkeys	Injury and cell changes in transitional and respiratory epithelium of nose. Shortened cilia, cell necrosis, secretory cell hyperplasia and inflammation at 6 days. Goblet cell hyperplasia by day 90.	Ambient O_3 can cause nasal cell injury and changes both in short and long term.	Harkema et al. (1987b)
118 490	0.06 0.25	0.06 ppm for 13 hr/day; slow 9 hr peak of 0.5 ppm, 5 days/wk; 1, 3 wks and 3 mo; recovery for 6 wks	F344 male rats	Shift from acute inflammatory phase to more chronic character. Increased cell volumes of Type I and especially Type II cells and interstitial cells. All except interstitial thickening subsided by postexposure 6 wks.	Interstitial inflammation may remain and lead to chronic matrix damage.	Huang et al. (1988)
294 588	0.15 0.30	8 hr/day; 6 or 90 days	Macaque monkeys	Respiratory bronchiolitis at 6 days, persisting to 90 days of exposure; nonciliated bronchiolar cells were hypertrophied and increased in number.	Persistent epithelial injury in respiratory bronchioles at O_3 concentrations as low as 0.15 ppm.	Hyde et al. (1988)
784 1254	0.40 0.64	8 hr/day for 90 days	Bonnet monkeys	Changes focused in respiratory bronchioles: (1) thicker walls, narrower lumens, (2) more cuboidal cells, fewer squamous, (3) thicker interstitium, (4) more cellular organelles associated with protein synthesis.	Concentration-dependent reactive peribronchiolar inflammation; apparent "adaptive" shift in cell populations.	Moffatt et al. (1987)
1117 2156	0.57 1.10	19 hr/day for 11 days; 1-60 day post-exposure	F344 female rats	At day 12, concentration dependent inflammation, Type II hyperplasia. Increased elastolygic/collagenlytic activities. Reduced intracellular collagenlysis. At 60 days, increased total collagen and modest alveolar ductal fibrosis.	Proteolysis and altered collagen turnover results in increased lung collagen after high O_3 levels.	Pickrell et al. (1987)
294 588 294	0.15 0.30 0.15	8 hr/day for 90 days 8 hr/day for 21 days	Bonnet monkeys	18:2 and 20:4 fatty acids in BAL increased ~2X in O_3 exposed monkeys; cholesteryl ester levels decreased and phosphatidylcholine increased with 90 day exposures. Lung PUFA levels decreased at 0.15 and 0.30 ppm while plasma LCAT activity increased at 0.3 ppm.	Changes in lung lipids may be related to O_3 and protection from oxidation by O_3.	Rao et al. (1985a,b)

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TABLE 5. (cont'd) CHRONIC OZONE EFFECTS IN EXPERIMENTAL ANIMALS

Ozone Concentration µg/m^3	Ozone Concentration ppm	Exposure Duration and Protocol	Species	Observed Effects	Conclusions	Reference
1196	0.61	8 hr/day for 1 yr	Cynomolgus monkeys	Increased lung collagen with altered crosslinking. Reducible crosslinks returned to control levels by 6 mo post; however, the nonreducible hydroxypyridinium remained elevated.	The collagen synthesized during exposure was abnormal, and once deposited remained irreversible.	Reiser et al. (1987)
588	0.3	7 hr/day; 5 days/wk for 6 wks	Swiss-Webster male mice	Greater increase in Type II cell area ($p = 0.08$) than number (n.s.).	Damage to Type I cells with Type II cell hyperplasia and possible alteration of lung connective tissue.	Sherwin and Richters (1985)
490	0.25	8 hr/day; alternating O_3/Air each of 18 mo vs. 18 mo continuous exposure	Cynomolgus monkeys	No major differences in lung volumes, body weights etc. Intermittent exposure group had lesions similar to continuous.	Episodic exposures had continued injury during non-exposure periods indicating higher risk than anticipated with lack of recovery.	Tyler et al. (1988)
235 490 980	0.12 0.25 0.50	21 hr/day for 6, 12 and 18 mo	F344 male rats	No increase in total lung collagen. No significant increase in ^3H protein incorporation into collagen and total protein in O_3 exposed rats.	Prolonged exposure to O_3 did not alter age-related changes in collagen synthesis rates or collagen content of the lung.	Wright et al. (1988)

the proximal bronchoalveolar junction (manuscript submitted for publication; see Chang et al., 1988). Augmentation of lavagable protein levels and tissue fractions of ascorbate and glutathione related enzymes after 12 months of O_3 exposure were indicative of the continued oxidant challenge. Further results of these studies through to 18 months of exposure and with recovery periods are anticipated by the end of 1988. The functional implications of these alterations in distal airway architecture have been explored in one higher-level O_3 study (0.5 ppm) in which airflow mechanics were reversibly altered (Gross and White, 1987). Lavagable enzymes in rats (Grose et al., 1988) and lipids in monkeys (Rao et al., 1985a,b) after prolonged exposures are consistent with shifting cell populations and/or inflammation, but remain non-specific effects that still need to be linked with progressive injury or adaptive adjustments to the challenge.

Initial data have been reported indicating that O_3 has a significant impact on nasal epithelium and mucosal lining (Harkema et al., 1987a,b). The health significance of this finding is uncertain, but is consistent with the deposition data on O_3 from both animal and human studies. Hence, though O_3 is relatively insoluble in water, the nose appears to provide some degree of scrubbing, and thus, providing protection to the deeper lung. Species differences in this capability are an important extrapolation question (see below).

3.1.3.3 Animal-to-Man Extrapolation--Recently reported studies and work in press cover two aspects of extrapolation: (1) models and their validation, and (2) species comparisons.

The Miller model (Miller et al., 1987a,b; Overton et al., 1987; Miller and Overton, 1988) of respiratory deposition of O_3 has been enhanced with the incorporation of both ventilatory parameters and empirically derived anatomical data (see Table 6). Use of the model with input parameters from several rodents and humans indicates preferential deposition, and presumably associated injury, in the bronchoalveolar junction which is consistent with empirical findings in laboratory animals. The model agrees well with the total and partitioned uptake values determined in human studies (Gerrity et al., 1988), though it fits less well with the rodent uptake data (Wiester et al., 1988). While the reasons for this are not as yet clear, the overall consistency of the predicted deposition distribution within the lung and the approximate equality of dose rate/surface area suggest that developmental work on the model is progressing properly (Gerrity and Wiester, 1987).

TABLE 6. NEW STUDIES RELEVANT TO POTENTIAL ANIMAL-TO-MAN EXTRAPOLATIONS

Ozone Concentration µg/m³	Ozone Concentration ppm	Exposure Duration and Protocol	Species	Observed Effects	Conclusions	Reference
	None		Rats Hamsters Baboons Humans	There were significant differences in lung levels of CAT, GSH S-trans, and GSH-Px-rats had greater deviation from the other 4 species.	Hamster is best model for human antioxidant enzymes.	Bryan and Jenkinson (1987)
588 784	0.3 0.4	0.3 ppm for 1 hr (rat) 0.4 ppm (human)	F344 male rats male humans	Total uptake in rats was approximately 44% of that inspired. Human uptake was 96% with 36% uptake in the nasopharynx. Estimated doses to lung surface of each species were about the same assuming nasal uptake in the rat of 20%.	Conclusions are preliminary but suggest that tissue dosing of lungs in rats and man may not be as difficult as might appear on the basis of total uptake.	Gerrity and Wiester (1987)
	None	Model	-	A mathematical model was used to quantitatively assess the impact of physiochemical (solubility, reactivity, diffusivity radial air phase transport) and physiological variables (lung size, ventilation rate) on the distribution of O_3 dose to the respiratory tract.	Liquid phase reactivity and surface liquid thickness contribute most to the O_3 tissue absorption rate and, therefore, to the determination of local tissue dose and its regional distribution.	Hanna et al. (1988)
1960	1.0	hr	Rabbits Rats Mice	Enrichment of ^{18}O in respiratory tracts of animals exposed to $^{18}O_3$, more in lining layer than whole tissue.	Tracing ^{18}O in tissues and tissue subfractions following $^{18}O_3$ exposure is feasible and practical.	Hatch and Aissa (1987)
392-3920	0.2-2.0	4 hr	Swiss Albino mice Sprague-Dawley rats N.Z. white rabbits Golden hamsters	BAL protein obtained after O_3 were most marked in guinea pigs ($\leq$0.2 ppm). Mice, rats, and hamsters at $\leq$1.0 ppm. Rabbits at 2.0 ppm. Not body weight/size dependent and not comparable in order of sensitivity to $COCl_2$.	There are species differences in sensitivity to O_3. Mechanisms not clear but antioxidants are not inversely correlated.	Hatch et al. (1986)
1960	1.0	2 hr ($^{18}O_3$) animals preexposed 1 yr to cycled 0.25 ppm O_3 5 days/wk	F344 male rats	Total respiratory uptake was determined by fractional uptake from inhaled gas. Deposition distribution in the nose, trachea, and deep lung were determined for ^{18}O distribution in those tissues. Total uptake was 54%; distribution was nasopharynx 44%; trachea 7%; lung 49%. No exposure group differences.	Approximately 44% of the inhaled O_3 was scrubbed by the nose of rats. Most of the remainder deposited in the pulmonary region. Chronic O_3 exposure did not affect uptake.	Hatch et al. (1988)

(continued on the following page)

TABLE 6. (cont'd) NEW STUDIES RELEVANT TO POTENTIAL ANIMAL-TO-MAN EXTRAPOLATIONS

Ozone Concentration		Exposure Duration and Protocol	Species	Observed Effects	Conclusions	Reference
µg/m³	ppm					
392-3920	0.2-2.0	Model	Rats Guinea pigs Rabbits Human Data	Model applied to human FEV_1 data and to BAL protein values for several rodents to compare tissue dose based response.	Guinea pigs appear most sensitive to O_3 on tissue dose basis. Humans appear to receive higher dose to elicit effect which creates potential conflicts in interpretation.	Miller et al. (1987a,b) Miller and Overton (1988)
	None	Model	Composite rat and guinea pig data	Theoretical model incorporates variety of factors associated with deposition in lower respiratory tract.	Major target for tissue dose is bronchiolar alveolar junction. Appears to be common across species and correlates with pathology.	Overton et al. (1987)
1960	1.0	Up to 1 hr; 24 hr post	Mice	$^{18}O_3$ used to track O_3 deposition; products accumulated linearly over 1 hr of exposure and were removed exponentially during the 24 hr after exposure.	^{18}O is a useful marker for O_3 exposure, accumulating linearly with time ($\leq$1 hr) at a single O_3 concentration. Reaction products are removed during recovery.	Santrock et al. (1988)
	None		Rabbits Guinea pigs Rats Hamsters Mice Humans Pigs Sheep	There were significant differences in lung levels of ascorbic acid, α-tocopherol and nonprotein-SH among the various species.		Slade et al. (1985)
588 1176 1960	0.3 0.6 1.0	1 hr	Sprague-Dawley rats, male	Total respiratory uptake of O_3 on a fractional basis was about 40%. The value did not change with exposure concencentration or over the normal range of tidal breathing.	Fractional uptake of O_3 in rats is about 40% of that concentration inhaled $\leq$1.0 ppm. While this uptake did not change, actual dose was concentration dependent.	Wiester et al. (1987)
588 1176	0.3 0.6	1 hr	F344, Sprague-Dawley and Long-Evans rats. Hartley guinea pigs.	Total respiratory uptake was about 42% for all species. Guinea pigs had uptake slightly but not significantly higher than the rats.	Fractional uptake of O_3 in rodents is about 42% and appears not to be species dependent.	Wiester et al. (1988)

Both human and animal uptake studies of O_3 have been conducted (see Tables 1 and 6). Although humans (Gerrity et al., 1988) appear to retain a somewhat greater fraction of the inhaled O_3 than do rodents (Wiester et al., 1988), the biological significance of this difference is uncertain at this time. Santrock et al. (1988) have shown that with continued exposure, products of O_3, as indicated by an [18]O label, accumulate in the lungs of mice with continued exposure. The difference in total uptake between humans and laboratory rodents may result in part from differences in nasopharyngeal removal of O_3 (40% in humans; 17% in rats, as reported by Hatch et al., 1988) resulting in shifts in regional doses in the two species (surface area differences and other factors are incorporated). Significant biological variations in lung tissue concentrations of several antioxidant enzymes have also been reported (Bryan and Jenkinson, 1987; Slade et al., 1985). How these antioxidants act individually or collectively as a defense against exogenous oxidants is not clear, however, since the five animal species tested for O_3 toxicity in concentration-response studies using BAL protein did not show corresponding variations in their sensitivities (Hatch et al., 1986). Thus, target dosimetry data, such as that being pursued with [18]O are needed, along with additional species sensitivity data to refine this issue. Nevertheless, the ability of the mathematical model to discern relative species sensitivities is encouraging despite its evolutionary state (Miller and Overton, 1988). Further work is still needed, however, to clarify various input components of the model, such as the roles of reactive surface fluid components and regional ventilation, for example, thereby ensuring its continued refinement and applicability to the extrapolation issue (Hanna et al., 1988).

3.1.3.4 Related Studies--An animal model has been developed (Costa et al., 1988b) that exhibits the same pattern of attenuated response to intermittent short-term O_3 (a phenomenon known as "adaptation") as has been described in man (see Table 7). This model demonstrates that morphological and biochemical changes continue even while lung dysfunction attenuates with repeated O_3 exposure, suggesting that the use of lung function tests alone to assess injury can result in misinterpretation of risk to health with repeated exposures to O_3. This does not rule out biological attenuation over a longer time period, but simply points out the gap in our knowledge in relating acute to chronic injury. Recently, Nikula et al. (1988a,b) showed that after 60 days (8 hr/night) of exposure to 0.96 ppm O_3 rat tracheal explants were significantly more

TABLE 7. RELATED STUDIES ON EXPERIMENTAL ANIMALS

Ozone Concentration μg/m^3	Ozone Concentration ppm	Exposure Duration and Protocol	Species	Observed Effects	Conclusions	Reference
686 1960	0.35 1.00	2.25 hr/day for 5 days with CO_2 augmented breathing.	F344 male rats	A pattern of lung function decrement occurred on days 1 and 2 of exposure and attenuated with repeated exposure as has been reported in man. Lung structural and biochemical changes did not behave similarly, but were constant or continued to progress.	Adaptation of lung dysfunction does not necessarily indicate the state of the underlying tissue.	Costa et al. (1988b)
1882	0.96	8 hr/night for 60 days with 3 ppm O_3 challenge.	Sprague Dawley rats	Cell populations examined after 60 days of exposure and challenged with 3 ppm O_3 *in vitro* showed adaptation/tolerance in preexposed cells.	Chronic tolerance can be induced ate the cellular level.	Nikula et al. (1988a,b)

resistant to the tissue necrosis produced by 3.0 ppm O_3 than were naive tracheal explants, suggesting that chronic "adaptation/tolerance" may in fact be real.

3.2 SUMMARY AND CONCLUSIONS: NEW HEALTH EFFECTS DATA

The following statements may be made on the basis of the preceding review of the newer health effects data now available.

1. Newer data from 1- and 2- hr controlled studies (Avol et al., 1987; Linn et al., 1986) add to existing concentration-response data indicating that lung function decrements and respiratory symptoms occur in children and young adults exposed for 1 to 2 hr to low O_3 concentrations ranging from 0.12 to 0.16 ppm while performing moderate to heavy exercise. Explanations for differences in lowest-observed-effects-levels among individuals and among cohorts include subject characteristics, exposure histories of subjects, and possible but presently unidentified differences in actual controlled exposure conditions.

2. In controlled studies, older subjects ($\geq$50 yr old) appear to have smaller changes in lung function than younger subjects when exposed to similar ozone concentrations (Bedi et al., 1988; Bedi and Horvath, 1987; Drechsler-Parks et al., 1987, 1988; Reisenauer et al., 1988). There were no significant differences between the responses of men and women to O_3 exposure for FEV_1 and FVC, although women had a significant increase in total respiratory resistance (Reisenauer et al., 1988). Since women had slightly lower mean exercise $\dot{V}_E$ during the studies, the data suggest that women may be somewhat more responsive to O_3 than men (Dreshsler-Parks et al., 1987; Reisenauer et al., 1988). The responses to O_3 may be less reproducible, however, in older than in younger adults (Bedi et al., 1988).

3. In more recent studies of adults with and without asthma (Kreit et al., 1988; Eschenbacher et al., 1988), both groups experienced similar responses to 0.4 ppm O_3 exposure, as indicated by decrements in standard spirometric pulmonary function tests and airway responsiveness to methacholine, but the changes were greater in asthmatics. Specific airway resistance was not increased in nonasthmatics, but in asthmatics nearly twice the increase was seen after exercise in O_3 versus air exposures. No symptom differences were seen between adult asthmatics and nonasthmatics. Pre- and post-ozone exposure challenge with methacholine may have confounded the results, however. Responses were also similar for adolescent asthmatics and nonasthmatics exposed to 0.12 and 0.18 ppm O_3 (Koenig et al., 1987, 1988), although a small but significant increase in $FEF_{50\%}$ was observed in asthmatics after 0.12 ppm O_3 exposure. In the adult nonasthmatics studied by Eschenbacher et al. (1988), indomethacin

pretreatment blocked the restrictive but not the airway reactivity component of the effects of O_3; a placebo effect was also observed in these nonasthmatics. A study by McDonnell et al. (1987) indicates that adults with allergic rhinitis show similar airway responsiveness to histamine after exposure to 0.18 ppm O_3 as a comparable group of nonallergic subjects. The only difference was a significant increase in airway resistance in the allergic subjects. It appears, therefore, that both allergic and asthmatic subjects have a greater increase in airway resistance after ozone exposure than do healthy subjects. The apparent order of airway responsiveness to O_3 from these studies is normal <allergic <asthmatic subjects.

4. Preliminary information suggests that interpretation of the results of controlled experimental ozone exposures should take into account whether frequent ambient exposure was a possibility during the period of study (Avol et al., 1988; Hackney and Linn, 1988; Hackney et al., 1988; Linn et al., 1988). This information also suggests that further work is still needed to resolve the implications of attenuation of pulmonary function responses to O_3. Subjects grouped according to their responses in the early spring to 0.18 ppm O_3 for 2 hr with intermittent exercise were tested the following fall, winter, and again the next spring. While "nonresponders" showed little seasonal variation in their response to O_3, "responders" showed attenuated responses in the fall, persistence of attenuation into the winter, and a return to their initial lung function responses to O_3 by the following spring. Many of the "responders" were reactive to methacholine and had histories of respiratory allergies and/or symptomatic complaints when previously exposed to smog.

5. Data from two newer studies (Gong et al., 1986; Schelegle and Adams, 1986) substantiate earlier findings that statistically significant reductions in maximal exercise performance may occur in well-conditioned athletes after performing continuous heavy exercise ($\dot{V}_E$ >80 L/min) for 1 hr at O_3 concentrations $\geq$0.18 ppm, but not at 0.12 ppm. Data from a third study (Linder et al., 1988) suggests that small decrements in maximal exercise performance may occur at O_3 concentrations <0.18 ppm, but limitations and questions concerning this study require further verification of the results. Environmental conditions such as high ambient temperature and/or relative humidity may affect subjective symptoms and may independently impair exercise performance such that differentiation between O_3-induced effects and effects of other environmental conditions may be difficult.

6. Controlled human studies of prolonged exposure (for up to 6.6 hr) to low O_3 concentrations ranging from 0.08 to 0.12 ppm report progressively larger pulmonary decrements and increased respiratory symptoms with increasing duration of exposure at moderate exercise levels ($\dot{V}_E$ = 40 L/min) (Folinsbee et al., 1988; Horstman et al., 1988a,b). They are similar in magnitude to those previously reported for healthy subjects performing heavy exercise ($\dot{V}_E$ >60 L/min) in high O_3 concentrations ($\geq$0.2 ppm) for shorter durations (≈2 hr).

7. New data show inflammatory and biochemical changes from exposures to moderately high levels (0.40 ppm) of O_3 for 2 hr with intermittent exercise ($\dot{V}_E$ = 70 L/min), as determined from bronchoalveolar lavage (BAL) 18 hr post-O_3-exposure (Koren et al., 1988a,b,c,d). Cells and enzymes capable of causing damage to pulmonary tissues, along with proteins involved in fibrotic and fibrinolytic processes, were increased at 18 hr post-exposure. Also, evidence of increased epithelial permeability (as determined by clearance of 99mTc-DPTA) was observed (Kehrl et al., 1987). Preliminary findings have been reported (Koren et al., 1988b) of elevated PMNs, also determined by BAL, in subjects exposed 6.6 hr to low levels of O_3 (0.1 ppm). Whether inflammation occurs following multihour exposures to lower O_3 levels remains unknown, but studies designed to determine this are now in progress.

8. Newer studies related to the dosimetry of O_3 show that differences in mode of breathing do not produce appreciable differences in fractional uptake of O_3 in the respective regions of the human respiratory tract. Increased frequency of breathing results in a decreased fractional removal of O_3 in both the upper (URT) and the lower respiratory tract (LRT), possibly as the result of decreased residence time in the airways and increased flow rate. The lowest fractional removal of O_3 in the URT occurred during nasal breathing, so that shifts from nasal to oronasal breathing resulting from exercise would somewhat offset increases in delivered dose caused by increased breathing frequency (Gerrity et al., 1988). Ozone-induced changes in tidal volume during 60-min, continous-exercise ($\dot{V}_E$ = 40 L/min) exposures to 0.4 ppm resulted in a slight reduction in total O_3 uptake (4%) and a larger reduction in LRT ozone uptake (9%). Thus, the typical ozone-induced reduction in tidal volume may protect the lower airways, with possible loss of that protection with recovery of normal tidal volume (Gerrity and McDonnell, 1988). Increased flow rates appear to reduce nasopharyngeal uptake (Gerrity, 1987). Additional modeling is need, however, to determine the effects of heavy exercise on regional dosimetry, especially on O_3 uptake in the LRT. These recent dosimetric data indicate that dosimetry modeling has progressed well in the past year or so. Additional data are still needed in other areas important to animal-to-man extrapolation, namely, tissue sensitivity and relative species sensitivities.

9. Newer epidemiological studies have employed numerous refinements over some of the older studies, in the form of: (a) better estimates of exposure, not just to ozone but also to other pollutants and other environmental variables that can confound or otherwise influence the outcome (e.g., Bates and Sizto, 1987; Spektor et al., 1988a,b; Raizenne et al., 1987); (b) use of serial measurements of pulmonary function for determining correlations with pollutants and other environmental variables (e.g., Raizenne et al., 1987, 1988; Spektor et al., 1988a,b); and (c) better biomedical characterization of cohorts (e.g., Raizenne et al., 1987, 1988; Gong et al., 1988).

10. Despite their refinements, however, newer epidemiologic studies have produced mixed results regarding the possible role of ozone versus the roles of other agents or factors in eliciting the functional decrements and/or rates of respiratory symptoms or respiratory disease observed. While functional decrements and respiratory symptoms have been shown in a number of studies to be statistically associated with ozone, other studies have shown them to be wholly attributable to particles (e.g., Dockery et al., 1988); or partially attributable to particles (e.g., Kinney, 1986); or partially attributable to other environmental factors such as ambient temperature or humidity (e.g., Spektor et al., 1988a) or even aeroallergens (e.g., Dockery et al., 1988; Gong et al., 1987).

11. Respiratory symptoms in epidemiologic studies have been reported not to occur in association with O_3 more often than such an association has been reported. Studies in which symptoms have not been reported at all following short (1-hr to multihour) daily exposures (over multiple days to multiple months) to ambient air containing ozone include (a) studies of children attending day or residential camps (Raizenne et al., 1987, 1988; Spektor et al., 1988a); (b) at least two panel studies (Dockery et al., 1988; Vedal et al., 1987); and (c) a study of adults exercising outdoors nearly every day (Spektor et al., 1988b). A recent reanalysis, using more widely accepted statistical approaches (Schwartz et al., 1988) of the Hammer et al. (1974) panel study of nurses in Los Angeles showed that cough was associated with O_3, but only at relatively high levels (well above 0.12 ppm). In a panel study of asthmatics (Gong, 1987), respiratory symptoms occurred during the study but did not correlate significantly with ozone overall and no worsening of symptoms attributable to O_3 occurred. (Multiple regression analysis of responses of those asthmatics in the top quartile for respiratory measures showed relationships between the respiratory measures and O_3, but these associations showed no dose-response pattern (Gong, 1987).)

12. Data reported from some of the newer epidemiologic studies show pulmonary function decrements that are as large or larger than those observed in human controlled (chamber) studies. Investigators have attributed these larger decrements as indicating, variously: (a) cumulative effects of O_3 occurring as the result of multihour exposures; (b) interactive effects of co-pollutants (additive or synergistic effects); (c) interactive or possibly independent effects of other environmental factors; (d) misspecification of true exposures, either because of inadequate dosimetry or other inadequacies in exposure characterization; and (e) possible persistence of effects from one day to the next.

13. Data showing such functional decrements have been reported in some recent studies (e.g., Raizenne et al., 1987, 1988; Spektor et al., 1988a,b; Kinney et al., 1988) in a manner intended to facilitate comparison of these decrements with those observed in

chamber studies. While it does permit easier comparison of epidemiologic findings with chamber-study data, this method of reporting also raises several questions that EPA believes must be investigated further before such findings can be taken at face value. Data on functional decrements have been reported as -ml/ppb O_3 for measures such as $FEV_{1.0}$ and FVC; and as -ml/sec/ppb for measures such as PEF and MMEF. Expression of data in this form assumes that: (a) O_3-induced changes in respiratory function are linear across all concentrations encountered in these studies (from zero up through episodic levels); and (b) the relationships among C, T, and $\dot{V}_E$ do not change with variations in these respective components of exposure. These assumptions are open to question. For example, the relationships between respiratory function changes and the respective components of exposure--C, T, and $\dot{V}_E$ --have not been tested at concentrations <0.08 ppm in chamber studies; and data obtained in chamber studies at the lowest concentration used (0.08 ppm) have not been modeled to determine whether changes in the influence of respective components are monotonic across ranges of C, T, or $\dot{V}_E$. Furthermore, questions of nonlinearities in the respective effects of C, T, and $\dot{V}_E$ on ozone-induced pulmonary function changes are far from resolved.

In Kinney et al. (1988), data from controlled (chamber) studies modeled by Hazucha (Hazucha, 1987; U.S. Environmental Protection Agency, 1986) were transformed and compared with data from five epidemiologic studies. The transformation assumed the applicability of a linear model even though Hazucha had fit data from controlled (chamber) studies to a quadratic model in describing changes in pulmonary function as a function of $\dot{V}_E$. Mean concentrations in the five epidemiologic studies were lower than the lowest concentration used in the controlled studies modeled.

14. In most of the epidemiologic studies, the collinearity of temperature and O_3 concentrations continues to cloud interpretation of study results. An additional factor confusing interpretation of epidemiologic results is the collinearity between exercise and total dose; i.e., exercise increases the total dose of ozone delivered to the respiratory tract and therefore the effects of exercise versus the effects of ozone dose are difficult to separate in epidemiologic studies. Subjects in chamber studies are usually better characterized before being studied than subjects in recent epidemiologic studies, who have generally been characterized by respiratory questionnaires but seldom by bronchial challenge or skin tests. Given the finding of apparently O_3-associated decrements in PEFR in some of the more recent studies, additional subject characterization to eliminate or reduce confounding by exercise-induced bronchospasm would be useful and would clear up some existing questions about the weight that can be placed on epidemiologic data that appear to be quantitatively consistent with chamber studies of 1-hr to multihour duration.

15. Three new studies on the effects in laboratory animals of multihour exposures to O_3 (Rombout et al., 1988; van Bree et al., 1988; Costa et al., 1988) report that exposure concentration (C) dominates duration of exposure (T) in eliciting O_3-induced changes in lavagable protein and antioxidant enzyme levels. Preliminary modeling efforts describing this data suggest that CxT interaction (synergism) occurs at decreased C and increased T; however, CxT relationships can only be applied at a given C and cannot be applied in general. The time of day of exposure is also an important determinant of oxidant toxicity since nocturnal exposures cause greater responses than do diurnal exposures. The primary determinants of O_3 toxicity are, therefore, exposure concentration and time of exposure followed by the duration of exposure.

16. New studies in monkeys and rodents support earlier findings that prolonged, repeated exposure to high concentrations of O_3 ($\geq$0.4 ppm) lead to the development of peribronchiolar inflammation (Barr et al., 1988; Moffatt et al., 1987), increased lung collagen content (Reiser et al., 1987; Pickrell et al., 1987; Hacker et al., 1986), and lung function changes (Gross and White, 1986, 1987). Even at lower O_3 concentrations (0.12 to 0.30 ppm), a lesion is still evident at the junction of the conducting airways and the gas exchange regions of the lung, characterized by cell population shifts along with interstitial inflammation and thickening (Huang et al., 1988; Barry and Crapo, 1985; Barry et al., 1985, 1988; Sherwin and Richters, 1985) but without increased lung collagen content (Wright et al., 1988; Filipowicz and McCauley, 1986) unless exposure is intermittent (Tyler et al., 1988). Preliminary information (Grose et al., 1988) from "episodic" exposure (0.19 ppm average concentration of O_3 over 9 hrs) of rats for 12 months indicates that significant decrements in lung function also occur at these lower O_3 concentrations that are consistent with early signs of focal fibrogenesis in this region of the lung. Increased lavagable lipids in monkeys (Rao et al., 1985a,b) found after prolonged exposure to ambient levels of O_3 (0.15 to 0.30 ppm) are also consistent with the shifting cell populations and/or inflammation reported at these concentrations. Multiple exposures to ambient levels of O_3 (0.15 and 0.30 ppm, 8 hr/day for 6 or 90 days) also cause injury and cellular changes in transitional and respiratory epithelium of the nose of nonhuman primates (Harkema et al., 1987a,b; Hyde et al., 1988).

17. Mathematical dosimetry models indicate preferential deposition of O_3 in the bronchoalveolar junction that is consistent with known laboratory animal data (Miller and Overton, 1988; Miller et al., 1987a,b; Overton et al., 1987). Further work is needed, however, to clarify various input components of the models, such as the roles of reactive surface fluid components and regional ventilation, for example, thereby insuring its continued refinement and applicability to the extrapolation issue (Hanna et al., 1988). Humans appear to retain a greater fraction (95%) of inhaled O_3 than do rodents (50%) but tissue dose rates/surface

area in each species may not be that different if nasopharyngeal partitioning is considered (Wiester et al., 1987, 1988; Gerrity and Wiester, 1987; Gerrity, 1987). Target dosimetry data, such as that being conducted with [18]O_3 (Hatch et al., 1988; Santrock et al., 1988; Aissa and Hatch, 1988; Hatch and Aissa, 1987) are needed, along with species sensitivity data (Bryan and Jenkinson, 1987; Hatch et al., 1986; Slade et al., 1985) to better refine this issue.

18. Laboratory animals exhibit a similar pattern of attenuated response to intermittent, short-term exposure as has been described in man (Costa et al., 1988b). Morphological and biochemical changes, however, even occur while lung dysfunction attenuates with repeated O_3 exposure, suggesting that the use of lung function tests alone to assess O_3-induced lung injury may result in misinterpretation of risk to the health of exposed individuals. More research is needed, therfore, to improve our knowledge of relationships between acute and chronic lung injury.

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